The Epidemiology of Infectious Diseases and an Outbreak in Queensland

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Master of Applied Epidemiology (MAE) Program

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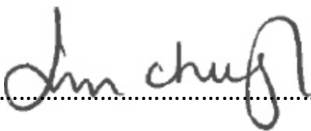
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Originality statement

'I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at Australian National University or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at Queensland Health or Queensland Children's Medical Research Institute, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation or linguistic expression is acknowledged'.

Signed………………………………………………………………………

Date……02 July 2016…………………………

Acknowledgements

I would like to thank my academic supervisor Kerri Viney for her patience and calm throughout the program, it was most appreciated and I was very thankful she was my supervisor.

I had wanted to be an epidemiologist for over ten years. There never seemed to be the right time to follow this dream until it was suggested I apply for a position in the MAE program. I am deeply grateful to my supervisors Dr Kerry-Ann O'Grady and A/Prof Stephen Lambert who encouraged me to apply and to then become my field supervisors.

I would like to thank the National Centre for Epidemiology and Population Health (NCEPH) for the fantastic opportunity to be part of such a great program. I found the MAE a challenging and very fulfilling experience.

I would like to express my gratitude to the rest of the 2014 cohort. I feel particularly fortunate to have been part of such a fantastic group of like-minded people. I will really miss course block and all of you, although Greg was never there much.

Thank you to Sheree Rablin for your friendship, support and encouragement over the years. You made the workplace super fun. Also thank you to Sarah Sheridan for numerous assistance with the pertussis and hepatitis A projects.

To my three beautiful boys I am most grateful for every day. Ross, thank you for believing in me. Thank you for your patience, humour and endless support in our crazy busy life. I would never have been able to complete this without you. Thank you little people Miles and Rohan for your words of encouragement ("I'm very proud of you mum!") and frank honesty ("mum, no offence but this is boring"). And yes, we can all go and play outside now.

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1.   Introduction

"Before you *believe* the results from any study, always say to them

LIAR, LIAR, LIAR!!

See if you can prove them wrong".

Mahomed Patel.

Overview of MAE experience

My MAE placement was a joint position between Queensland Children's Medical Research Institute (QCMRI) and the Communicable Diseases Branch (CDB) of Queensland Health (QH) both located at Herston in Brisbane.

During my placement at QCMRI, formerly located on the grounds within the old Royal Children's Hospital at Herston, Brisbane, we moved offices at least three times. The Edith Cavell building was a two-story beautiful old heritage listed building that used to be the nurses quarters. Unfortunately storm season damaged the building on a regular basis to the point where it became uninhabitable. At the same time, construction of the new Lady Cilento Children's Hospital at South Brisbane was underway with the Centre for Children's Health Research (CCHR) on the same campus. The CCHR, where QCMRI is now located, is a beautiful new building with spectacular views over South Bank and the Brisbane River. And storm proof, hopefully.

My QCMRI placement was within the Respiratory Infection Outreach And Research team (RiOAR), not to be confused with the Brisbane Roar soccer team. My supervisor for this placement was Dr Kerry-Ann O'Grady who was the group leader. Within our team were many other students, all with different research projects underway which was an exciting space to be. My supervisor for my QH placement was A/Prof Stephen Lambert who was also located in Edith Cavell and then CCHR building once we moved.

During my placement I was able to spend a short time at one of the busiest public health units in South Brisbane for my outbreak investigation project. This was a fun, dynamic unit with a very experienced team of public health epidemiologists and I learned a great deal in a short period of time there.

Kerri Viney was my academic supervisor through the National Centre for Epidemiology and Population Health (NCEPH) located at the Australian National University in Canberra. Kerri was a great fit for me. She was a grounded, supportive helpful supervisor and never made me feel like my questions were stupid when in hindsight they probably were!

Summary of public health experience

Epidemiological study (Chapter 2)

In Australia, influenza vaccination is recommended for all pregnant women. Evidence to date suggests influenza vaccination has not been associated with adverse birth outcomes, however there are still concerns about safety and risks of receiving a vaccine during pregnancy. This chapter describes a nested retrospective cohort study comprising 7,121 mother-infant pairs in Australia from 2012-2014. The study focussed on whether mothers who had received an influenza vaccination during pregnancy had poorer birth outcomes compared to unvaccinated women in pregnancy. Birth outcomes examined were infant birthweights and prematurity. I found there were no differences in birth outcomes between the vaccinated and unvaccinated groups. This was the first Australian study examining birth outcomes of influenza vaccination during pregnancy and as such, results will make an important contribution to the literature on this topic.

Analysis of a public health dataset (Chapter 3)

Morbidity and mortality of pertussis is highest in infants under six months of age. Control efforts focus on preventing disease in this age group by minimizing exposure by other infected cases. This project presents results from a retrospective case series analysis of all valid and probable pertussis notifications in Queensland from 1997-2014 by age group. Over this 18 year observation period, amongst children less than three years of age, notifications of pertussis were most common amongst infants <4 months of age. Increases in pertussis notifications from 2009 coincided with a substantial increase in the number of cases diagnosed by PCR. The results in this case series are consistent with that of overseas literature. It will important to monitor the outcomes of the implementation of the Queensland maternal pertussis vaccination program which commenced on 01 August 2014 regarding pertussis notifications in infants less than four months of age.

Outbreak investigation (Chapter 4)

This chapter describes an outbreak investigation of 85 confirmed cases of *Salmonella* Typhimurium (MLVA 03-12-11-12-524 and MLVA 03-13-11-12-524) in South-East Brisbane in January 2015. Cases experienced gastrointestinal illness following the consumption of Kim Bap (Korean style sushi). The descriptive study involved epidemiological, laboratory and environmental investigations. Twenty-two cases were hospitalised, seven of these (32%) were children. The likely vehicle of transmission of infection for this outbreak (Kim Bap sushi) was distributed by one producer to multiple food retail outlets in South-East Brisbane. Once supply of this product had ceased there were no further reported cases of illness. I was unable to determine any associations between food exposures and illness due to the absence of a comparison group.

Evaluation of a surveillance system (Chapter 5)

Hepatitis A virus (HAV) in Australia remains a nationally notifiable disease and control is considered to be a high public health priority. This evaluation of the current surveillance system for HAV in Queensland examined acceptability and timeliness. A detailed retrospective case series data analysis and genotype analysis was also conducted to determine sensitivity, representativeness and data quality. Age and sex data were complete, however risk factor data were largely incomplete. Data quality for travel history, post exposure prophylaxis vaccination, Indigenous status, mechanism of infection and hospitalisations were poor. Most cases of HAV are now acquired as a result of overseas travel or exposure to a returning overseas traveller. The timeliness of all aspects of the current system is reassuring however there needs to be a sustained improvement in completeness of data at every step, particularly for identification of Aboriginal and Torres Strait Islander people and for risk factor data.

Presentations

1. FluMum birth outcomes 2012-2014, Communicable Disease Control conference June 2015, Brisbane. Oral presentation. Appendix 2.3

2. The epidemiology of hepatitis A in Queensland 1988-2014, Communicable Disease Control conference June 2015, Brisbane. Oral presentation. Appendix 5.1

3. FluMum birth outcomes 2012-2014, National Centre for Epidemiology and Population Health seminar March 2015, Canberra. Oral presentation. Appendix 2.3

4. Presentation of birth outcomes results to a lay audience QCMRI in-service, June 2015, Brisbane. Appendix 2.3

Publication submitted to peer reviewed journal

1. **McHugh L**, Neill AS, Bates J, Slinko VG, Bell RJ, Barten J and Jarvinen K. *Outbreak investigation report of* Salmonella *Typhimurium following consumption of Korean style sushi in Southside Brisbane, January 2015*. Accepted for publication in CDI journal June 2016.

2. *Epidemiology project: Birth outcomes for Australian mother-infant pairs who self-reported receiving an influenza vaccine during pregnancy, 2012-2014.*

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Prologue

I had been employed as the national coordinator of the prospective cohort study 'FluMum' when I was accepted into the MAE program. My main career interest is in perinatal epidemiology so I was very keen to remain involved in the study and examine birth outcomes for my epidemiology project. Being involved from the conception of this study to the final delivery has been very rewarding.

My Role

My part in this project involved developing a nested dataset to analyse national birth outcomes of the FluMum study. It involved; writing a protocol and adapting a study participant questionnaire, attending chief investigator meetings and conducting data linkage of laboratory confirmed influenza for six study sites through the state health departments. I was invited to present preliminary results of this study to my peers at the NCEPH seminar series during March 2015 courseblock. I was also accepted to give an oral presentation at the 2015 Communicable Disease Control conference in Brisbane which fulfilled a core component of the MAE program. A draft paper of the results from this study is in preparation for submission to a scientific journal which also fulfils a core component of the MAE program.

Lessons Learned

One very unexpected but grateful outcome that arose from this project was data analysis skills. I never dreamed I would be someone who could use the statistical data analysis program 'Stata'. Really use it. Having gone from someone who was scared of do-files to creating my very own 'sophisticated' (not my words) do-file to perform the analysis component of this project makes me feel very proud. I would like to acknowledge Ross Andrews for his limitless patience and lightning quick responses to my 'tiny' opportunistic Stata queries. I hope I have taught him something too. Another unexpected outcome was finding myself using terminology such as 'compared to what?', 'it depends' and 'within cohort comparisons' and thinking to myself 'what's my denominator'…I am finally starting to feel like a real epidemiologist.

Prologue

Public Health Implications

Maternal influenza vaccine uptake is a public health policy initiative that has been advocated for more than a decade without any systematic initiatives to monitor implementation or birth outcomes.[1] Providing further evidence around the safety of receiving a vaccine during pregnancy, particularly infant birthweights and prematurity may help increase uptake of the vaccine. This may reduce the morbidity and mortality that results from influenza infection when it occurs during pregnancy.[2]

Acknowledgements

I would like to acknowledge the FluMum investigator team for their support of me doing this project as well as the study coordinators at each of the 'FluMum' sites around the country who were responsible for the excellent quality of data collected.

Abstract

Introduction

Influenza vaccination is recommended for women who will be pregnant during the influenza season. Safety and effectiveness are key influences of vaccine uptake for both vaccine providers and parents. While the evidence to date suggests influenza vaccination has not been associated with adverse birth outcomes, there are still concerns about safety and risks of receiving a vaccine during pregnancy. To date there have been no studies or systematic reviews that have been large enough to exclude risks of relatively rare adverse events. My epidemiology project is part of an ongoing national cohort study 'FluMum' and comprised over 7, 120 participants. To date it is the largest cohort of mother-infant pairs in Australia. I aimed to assess the relationship between receiving an influenza vaccination during pregnancy and prematurity and infant birthweight.

Methods

I conducted a nested retrospective cohort study using data collected between 01 April 2012 and 31 December 2014 from the overarching 'FluMum' study. These data were from mother-infant pairs at time of enrolment. The primary exposure of interest for this nested study was self-reported receipt of an influenza vaccination during pregnancy. The primary outcomes of interest were birthweights in grams of infants and gestations in weeks of the mother at time of birth of the infant. The primary analyses were comparisons of these birth outcomes between mothers who received an influenza vaccine during pregnancy with unvaccinated mothers. Maternal co-morbidities and risk factors for influenza infection were also examined

Results

I found there were no differences in birth outcomes between the vaccinated and unvaccinated groups. Of the 7,121 mother-infant pairs who were enrolled in the study, the mean maternal age was 31.7 years. The mean gestation at birth was 38.7 weeks for both groups; mean birthweight was 3332 grams whilst 52% of infants were male. The ratio of maternally vaccinated:unvaccinated participants was 1:1.9 (34% v 66%)

Conclusion

This is the first Australian study examining birth outcomes of influenza vaccination during pregnancy and as such, these results will make an important contribution to the literature on this topic. The birth outcomes results arising from this study are reassuring. In relation to the safety of receiving a maternal influenza it can be deemed appropriate to offer the vaccine to all pregnant women in accordance with the current recommendations in Australia.

Introduction

Influenza is an acute viral illness affecting the respiratory tract and can be highly infectious.[3] There are three major strains; influenza A, B and C. The A and B strains cause significant seasonal morbidity and mortality but are potentially vaccine preventable.[4] Severity of symptoms vary but influenza generally causes fever, headache, dry cough, fatigue and sore throat.[3] The disease severity is highest in infants, the elderly and pregnant women.[4]

Worldwide, influenza infection during pregnancy causes increased morbidity and higher rates of hospitalisation than those of the general population, especially for women with pre-existing respiratory conditions like asthma and bronchitis.[4] During influenza pandemics, 50% of the deaths that occurred among women of child-bearing age were amongst pregnant women.[2] Elevated morbidity and mortality rates were evident during the 2009 (H1N1) influenza pandemic, which increased the emphasis on pregnant women being deemed a priority group for vaccination both in Australia and overseas.[5-8]

Influenza vaccination is recommended for women who will be pregnant during the influenza season.[8] Safety and effectiveness are key influences of vaccine uptake for both vaccine providers and parents.[9] While the evidence to date suggests influenza vaccination has not been associated with adverse birth outcomes,[10-14] there are still concerns about safety and risks of receiving a vaccine during pregnancy.[9] A systematic review on the safety of maternal vaccination did not find evidence of increased risks of adverse birth outcomes following vaccination.[14] Other studies infer the same message regarding safety of maternal vaccination and birth outcomes however there have been no studies or systematic reviews that have been large enough to exclude risks of relatively rare adverse events.[11-13,15-18]

In Australia, maternal influenza vaccination during pregnancy is recognised as the primary strategy to prevent influenza illness during pregnancy. It is a public health policy initiative that has been advocated for more than a decade by Commonwealth and State Governments.[8] However despite this, there have been no systematic initiatives employed to monitor its implementation or assess birth outcomes.[1] I

conducted a nested study which focussed on the safety of receiving an influenza vaccine during pregnancy with respect to infant birthweights and prematurity. If there is evidence that antenatal vaccination is safe in terms of these birth outcomes in the Australian context, this may facilitate increased uptake of the vaccine during pregnancy.

Literature review

Description of search methods

I conducted a literature search of SCOPUS and PubMed databases using the search terms "Safety of influenza vaccine in pregnancy" AND "Birth Outcomes" AND "Australia". This yielded zero results. I then removed "safety of" to broaden the search. This also produced no results. After I removed "Australia", the modified search then yielded a total of 161 articles (Figure 2.1).

I then refined the search terms and restrictions. This involved excluding; articles in another language other than English, laboratory based studies, case reports, letters, comments, editorials and book chapters. This search yielded 96 results. Given that new and emerging research is being conducted in maternal vaccination, I further limited the search to publication dates since the year 2007. I scanned these for duplicates and relevance, then produced a shortlist of six unique articles, which I subsequently evaluated and synthesized (Table 2.1).

Figure 2.1:   Literature review flowchart with number of results for searches of birth outcomes and influenza vaccine in pregnancy in Australia in PubMed and Scopus, 2015.
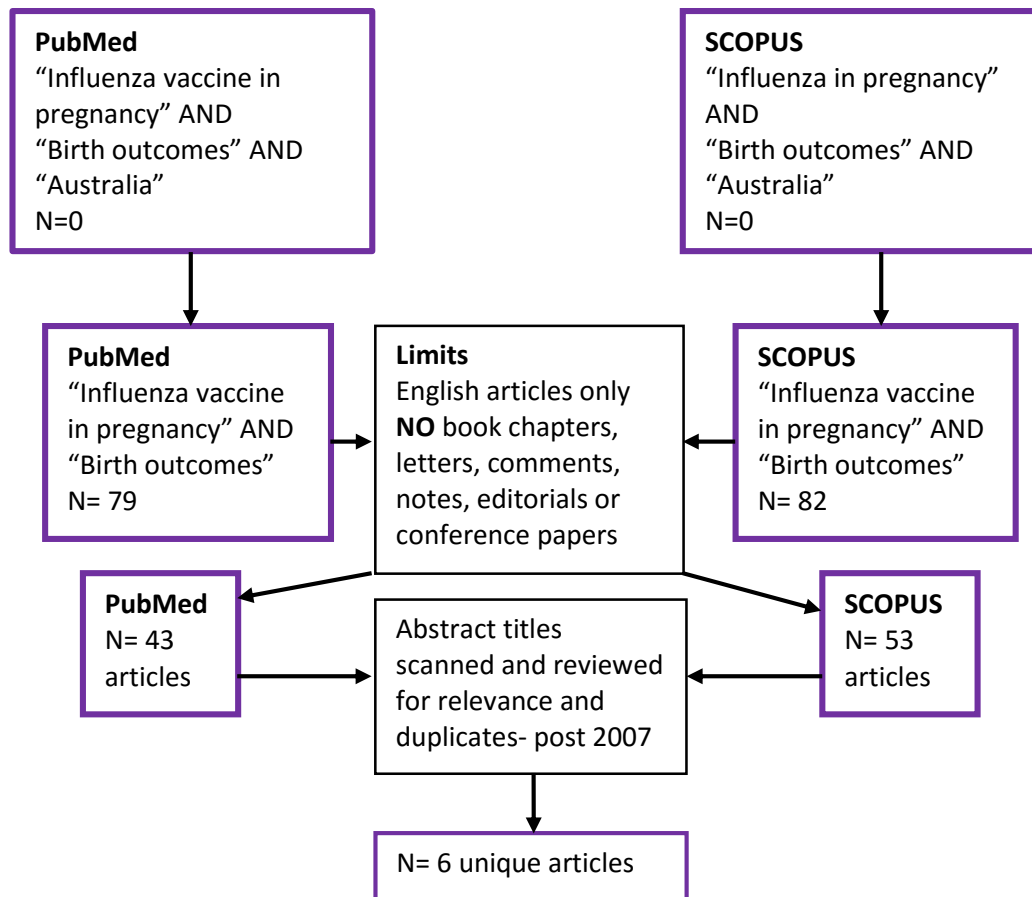
Table 2.1:   **Summary of research articles on maternal vaccination safety, 2007-2015**

Author, Year	Study Design	Sample Size	Country	Study Objective	Key results
Tamma et al., 2009	Systematic review	11 studies, 96,027 participants	USA	Safety of maternal vaccination	No increased risk of adverse birth outcomes
Bratton et al., 2014	Meta-analysis	7 studies, 116,001 participants	USA	Birth outcomes-safety	No differences in stillbirths or spontaneous abortions
Sheffield et al., 2012	Retrospective cohort	10,225 participants	USA	Birth outcomes-safety of 1st trimester influenza vaccination	No differences in birth outcomes
Legge et al., 2014	Retrospective data analysis	12,223 participants	Canada	Safety of maternal influenza vaccination-neonatal outcomes	No increased risk of adverse birth or neonatal outcomes. Stillbirth data not included in the analysis
Omer et al., 2011	Retrospective cohort analysis	4,168 participants	USA	Birth outcomes-safety	Immunisation provided protection against prematurity and low birthweight
Pasternak et al., 2012	Registry based data analysis	53,432 participants	Denmark	Birth outcomes-safety of 2009 H1N1 pandemic vaccine	No differences in adverse birth outcomes with influenza vaccination during pregnancy

A systematic review by Tamma et al.,[11] found no adverse birth outcomes using data pooled from eleven studies following maternal influenza vaccination during pregnancy. The birth outcomes examined in this review included prematurity, birthweights of infants, rates of caesarean sections, congenital anomalies and neonatal morbidity and

Apgar scores. A large proportion of the studies included in the systematic review were greater than ten years old however, and sample sizes were small with one study having no control group. All of the studies included in this systematic review occurred before the 2009 H1N1 influenza pandemic and none of the studies were conducted in the Southern hemisphere.

Bratton et al.,[14] conducted a systematic review and meta-analysis using seven studies and found no increased risk of stillbirth or spontaneous abortion in women who received an influenza vaccine during their pregnancy compared to unvaccinated pregnant women. The study design for six out of seven of these articles reviewed were cohort studies with large sample sizes and hence power to detect an association between receipt of vaccination during pregnancy and fetal loss on an individual study basis. However, power was diminished when these studies were pooled for the meta-analysis and only one study adequately captured potential confounding factors. There were no validation data collected for trimester of pregnancy for receipt of influenza vaccination which is important when assessing risk and determining whether the vaccine was given prior to, or following fetal loss. The analyses were heavily based on one specific vaccine used during the 2009 H1N1 influenza pandemic and not seasonal influenza vaccines, therefore comparisons cannot reliably be made nor conclusions drawn.[19] Stated limitations by authors of both the systematic review and meta-analysis included the use of databases as well as population registries with potential high risks of selection and measurement biases.

A retrospective cohort study by Sheffield et al., in the USA assessed the safety of first trimester receipt of an influenza vaccination on birth outcomes such as stillbirths, neonatal deaths, prematurity and congenital malformations.[12] There was no evidence of differences in birth outcomes between the vaccinated and unvaccinated pregnancy cohort. This study was well powered due to the large sample size and a comprehensive list of potential confounding factors were collected from the participants and included in the analyses. There were large numbers of high-risk participants in this study who would normally be targeted for influenza vaccination during pregnancy due to increased risks of complications. Also, this study offered influenza vaccination free to all enrolled participants, further increasing potential selection bias. Vaccination status

was obtained from hospital records at the recruitment site, which may have resulted in some women being incorrectly classified as unvaccinated if an influenza vaccination in pregnancy was received from a source other than the hospital. Due to the large sample size though, any difference in significance would have been minimal.

Population-based retrospective data analysed by Legge et al.,[13] examined birth and neonatal outcomes of influenza vaccinated and unvaccinated women in pregnancy from one province in Canada. This was a large sample size (12,233) and therefore well powered. The results found a protective effect of receiving an influenza vaccine during pregnancy in relation to birthweights, prematurity and babies that were small for gestational age which is consistent with the literature. Legge et al. collected data on livebirths and stillbirths but excluded stillbirths from the analysis.[13] For safety statistics, it may have been useful to know the proportions of mothers who had birthed a stillborn baby and received influenza vaccine during pregnancy compared to those who delivered a stillbirth and not received a vaccination though numbers would have been small. Dates of receipt of maternal vaccination were also unavailable for this study so validation of influenza vaccine being administered and trimester of pregnancy was unable to be determined. Again as with other studies, absence of trimester of vaccination status hinders the ability to establish whether influenza vaccine was administered prior to, or following any adverse fetal or maternal outcomes, or assess whether there are differences in perinatal outcomes depending on the trimester of vaccination given.

Consistent with other studies presented in this literature review, safety studies in the US by Omer et al.,[6,18] and in Denmark by Pasternak et al.,[20] analysed birth outcomes such as prematurity, birth defects and birthweights. These studies found no increased risk of adverse outcomes from receiving an influenza vaccination during pregnancy and indeed showed a protective effect of receiving the vaccine during pregnancy in relation to low birth weights, prematurity and rates of stillbirth. This is also consistent with current literature available.

Whilst there is evidence from the Northern hemisphere that maternal influenza vaccination during pregnancy is not associated with adverse birth outcomes such as

prematurity, low birthweight and stillbirth,[14] there are no Australian data on this topic. A limitation of the studies from Europe and the US has been inadequate availability of data on the timing of maternal influenza vaccination during pregnancy, specifically the trimester of vaccination.

Aims

This study aims to inform maternal influenza vaccination policy and strategies by demonstrating whether women in Australia who self-reported receiving an influenza vaccine during any stage of pregnancy were:

a) more likely to birth smaller infants compared to mothers who did not receive an influenza vaccine during pregnancy and,

b) more likely to birth infants who were more premature compared to mothers who self-reported they did not receive an influenza vaccine during pregnancy.

Objectives

Amongst mother-infant pairs in Australia, the primary objectives of my study were to compare birth outcomes between the exposed (infants born to mothers who self-reported they had received influenza vaccination during any stage of their pregnancy) and the unexposed (infants born to mothers who did not self-report receipt of influenza vaccination during their pregnancy) where the primary outcomes of interest were:

a) infant birthweight (grams); and
b) gestation at birth (weeks)

The secondary objectives were to:

a) compare maternal characteristics between women who self-reported receipt of an influenza vaccine during pregnancy with those who did not
b) compare maternal risk factors for influenza between women who self-reported receipt of an influenza vaccine during pregnancy with those who did not
c) compare birth outcomes (birthweight and gestation) by trimester of vaccination within the exposed group (that is women who reported receipt of an influenza vaccine during pregnancy), compared to women who did not receive an influenza vaccination during pregnancy.

Methods

Study design and population

The study design for this FluMum birth outcomes project was a retrospective nested cohort study. The methods for the overarching study, called 'FluMum', have been published.[1] In brief, 'FluMum' is an ongoing national prospective cohort study where mother-infant pairs were recruited at or soon after birth (when vaccine exposure during pregnancy was ascertained) with the mother-infant pairs followed through until infants reached six months of age. Participants were enrolled from public and private maternity units, immunisation centres and/or maternal and infant health centres in six participating Australian cities; Darwin, Brisbane, Sydney, Melbourne, Adelaide and Perth. My study was nested within that overarching study as a retrospective cohort, utilising the data collected at or soon after delivery.

Ethical considerations

Written informed consent encompassing all aspects of this nested study was obtained from all enrolled participants of the original FluMum cohort study. Data were kept in a de-identified format in a password protected computer within a locked facility. No identifiable information has been or will be presented in any aspect of the study results. Participant confidentiality and privacy was maintained at all times.

The results for participants who identify as Aboriginal and or Torres Strait Islander, under the variable 'Indigenous status', have been presented at a state and territory level only, rather than at a local, regional or remote community level. This is to protect identity and ensures confidentiality is maintained as numbers of Aboriginal and or Torres Strait Islander peoples are small in this study.

The FluMum study was approved by all state and territory ethics committees at the sites involved, as well as unconditional ethics approval from the Australian National University.

My nested study involved no physical risks to any participant as there were no blood tests, specimen collections or injections involved. There was no further contact with any participants at any stage of the nested project beyond the initial questionnaire and 6 month follow-up conducted by trained study staff as a component of the overarching study. All data will be archived and then destroyed after 5 years.

Figure 2.2: **Study design of FluMum nested retrospective cohort study (by outcome) and self-reported receipt of influenza vaccine during pregnancy in mother-infant pairs, Australia (2012-2014).**
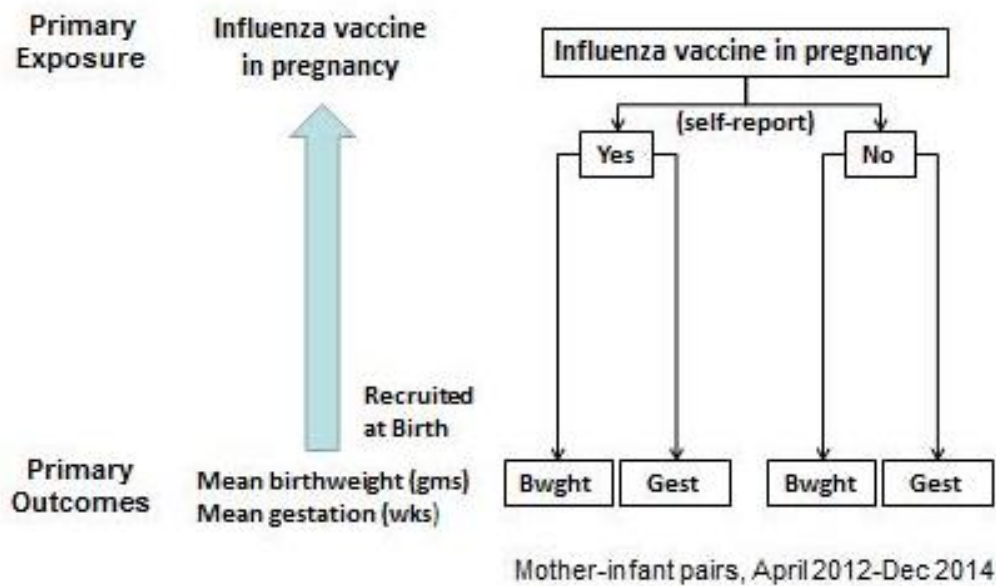
For my study, I only included data collected between 01 April 2012 and 31 December 2014 on the mother-infant pairs at time of enrolment in FluMum given that study was not due to finish recruitment until October 2015. As an existing dataset, the number of enrolled participants was pre determined and dependent on the number of enrolled participants in the overarching FluMum study at 31 December 2014.

Inclusion criteria

The study population came from formally consented mothers who were over the age of 17 years, able to understand and speak sufficient verbal English, and had birthed a live born infant.

Exclusion criteria

For my study, I excluded mothers from the dataset if they had received an influenza vaccine 14 days or less prior to the birth of their infant. Mothers who had birthed a stillborn infant were not approached to be in the study. This was a requirement by most of the participating sites' ethics committees.

Multiple births were recorded in the original dataset of the overarching FluMum study but were excluded from this analysis due to outcome variables only being recorded on the first born child. Multiple pregnancies are also a potential confounding factor for both birthweight and gestation at birth as these infants are generally smaller in grams and often do not go to full term.[21]

Primary exposure of interest

The primary exposure of interest for this nested study was self-reported receipt of an influenza vaccination during pregnancy. The ratio of exposed:unexposed participants within the nested study was expected to be 1:2 based on preliminary analyses of the national FluMum data suggesting approximately 30% of women enrolled reported receipt of an influenza vaccine during pregnancy (Andrews, unpublished data, personal communication, 2014) .

Primary outcomes of interest

The primary outcomes of interest were:

   a) infant birthweight in grams, and;
   b) number of weeks gestation at delivery of the infant.

Based on definitions from the Australian Institute of Health and Welfare (AIHW) Mother's and babies report,[22] prematurity was defined as any infant born before 37 completed weeks of gestation and low birthweight was defined as any infant born less than 2500 grams.

A singleton infant born before 35 completed weeks gestation was defined as being 'very premature', whilst a singleton infant born before 30 completed weeks gestation was defined as 'extreme prematurity'.[22]

'Very low' birthweight, and 'extremely low' birthweight, as defined by the World Health Organization (WHO) were infants weighing less than 1500 grams at birth and infants weighing less than 1000 grams at birth respectively.[4]

Gestation in weeks at birth of the infant and birthweight in grams of the infant were self-reported by the mother. Where data were available on the variable 'last normal menstrual period' (LNMP), this was used to cross check against self-report of the gestation (in weeks) at birth of the infant. To cross check these data, I calculated the difference between the infant date of birth and the LNMP date to give weeks gestation at birth. Where illogical differences in dates were found, research staff at relevant study sites were asked to review the original questionnaire to cross check dates. This also provided an opportunity to correct data entry errors at the study sites.

Data collection and storage

Data were collected and entered on all maternal and infant characteristics by trained researchers. The researchers conducted face to face interviews using a detailed, structured participant questionnaire (Appendix 2.1). All FluMum study data were stored electronically in a de-identified format in a purpose-built, password protected Filemaker Pro Advanced V13 (Filemaker, Inc. Santa Clara, USA) relational database.

Data included in the analysis

Table 2.2 contains the variables collected for analysis. These variables were chosen to compare baseline demographic characteristics of the mother as well as to capture risk factor data and potential confounders. A number of maternal comorbidities and risk factors for acquiring influenza infection are listed in the Australian Immunisation Handbook.[8] These factors, outlined in Table 2.3, were all included in our analysis. The variable on diabetes mellitus included type one, type two and gestational diabetes. Data were recorded collectively for this variable and not analysed separately for each individual type of diabetes. Baseline characteristics assessed for the infant were sex and whether the baby had been identified as being of Aboriginal or Torres Strait Islander origin.

Table 2.2:   Variables included in data collection for FluMum analysis

Variable	Workbook (Appendix 2.1)
Maternal age in years at birth of infant	Q2.03,12.01
Aboriginal and Torres Strait Islander status	Q18.01
Country of birth of mother	Q18.04
English as a primary language spoken at home	Q18.06
Gestation in weeks when mother 1st received antenatal care	Q4.02
Any previous influenza vaccinations received	Q10.01,11.01
Maternal respiratory illness during pregnancy	Q4.06-6.11
Maternal smoking status during pregnancy	Q17.13
Exposure to indoor tobacco smoke during pregnancy	Q18.16
Exposure to household tobacco smoke during pregnancy	Q18.15
Household occupancy- how many people usually live in the house	Q18.08
Lives in household with other children who attend daycare, preschool or kindergarten (excluding the birth infant)	Q18.14
Educational qualifications of mother	Q19.01
Place of birth of infant- public hospital or private hospital	Screening Form

Table 2.3: **Maternal co-morbidities and risk factors for influenza infection examined in the FluMum study participants, Australia, 2012-2014.**

Co-morbidities and risk factors for influenza infection	Workbook (Appendix 2.1)
Heart disease	Q17.01
High blood pressure or hypertension*	Q17.02
Any severe pneumonia requiring hospitalisation	Q17.03
Chronic respiratory conditions†	Q17.04
Immunosuppressive conditions‡	Q17.05
Cancer requiring treatment	Q17.09
Diabetes mellitus§	Q17.10
Regular use of immunosuppressive medication	Q17.11
ANY co-morbidity/risk factors‖	As above

* Including essential hypertension, gestational hypertension and pre- eclampsia
† Including emphysema or severe asthma requiring frequent hospital visits
‡ Including HIV/AIDS
§ Including type 1, type 2 and gestational diabetes
‖ Results of pooled risk factors and comorbidities

Statistical methods

Primary analysis

The primary analyses were comparisons of birth outcomes between mothers who self-reported receiving an influenza vaccine during pregnancy with those mothers who self-reported not receiving an influenza vaccine during pregnancy.

Secondary analysis

Maternal comorbidities and risk factors for influenza were assessed individually to determine whether there were any differences between women who self-reported influenza vaccination in pregnancy compared to women who self-reported that they did not have an influenza vaccine in pregnancy. If a woman was unsure of her vaccination status during pregnancy then she was excluded from these analyses. These co-morbidities and risk factors were then grouped together as a new variable called 'ANY comorbidity/risk factor'. This was to determine whether there were any within cohort differences between the two groups as any person with any of these co-

morbidities and risk factors listed in the 2013 Australian immunisation handbook are recommended to receive an influenza vaccination annually (regardless of their pregnancy status).[8]

Data cleaning

Data were extracted from the Filemaker Pro Advanced relational database for analysis. Missing data were coded as such, and data cleaning, recoding, labelling and analyses were conducted and documented in my Stata do-file (see Appendix 2.2). The data were analysed using StataCorp v.12.1 (StataCorp, Texas).

Analysis

Baseline characteristics

Demographic data on all remaining eligible participants were examined to determine whether there were any differences between the vaccinated and unvaccinated group. Results were presented as descriptive statistics (means, proportions and their corresponding 95% confidence intervals (CI).

Univariable analysis

Two-sample t-tests were calculated for continuous variables to determine whether there were any differences in mean birthweights and mean gestations at birth of the infants. Means were calculated instead of medians due to the distribution of the data. Differences in means were calculated and 95% CI's for the differences between these means. Chi-squared tests were calculated for binary and categorical variables and a Fisher's exact test was conducted on cells that had less than five expected cases. Relative risks, 95% CI's and risk differences were performed on the binary and categorical variables in order to determine whether there were any statistically significant and clinically relevant differences between the two groups. Differences were considered to be statistically significant if the corresponding p-values were less than 0.05 and 95% CI's did not cross 1.

Multivariable analysis

Regression analyses, interactions, subgroups and sensitivity analyses were proposed as part of the analysis plan. However, these have not been conducted as yet. Multivariable analyses will plan to examine for the presence of potential confounding factors known to cause reduced birthweights and preterm births. Specifically, these will include the variables 'hypertension', 'diabetes mellitus', 'ANY comorbidity/risk factor' and smoking exposures during pregnancy.

Results

Between 01 April 2012 – 31 December 2014, there were 10,398 women screened for eligibility to participate in the FluMum study. Of these, 3229 (31%) were deemed ineligible and/or declined participation. Amongst those participants who were eligible and provided consent (n = 7,169), 48 (0.7%) were withdrawn either because the participant withdrew consent or because of a death of the baby or the mother. The final dataset included 7,121/10,398 (68%) women for analysis. Participants were evenly distributed between the six participating Australian sites (Figure 2.3). Participant characteristics were similar between women who did and did not provide consent however data on maternal age was not collected routinely from all sites if participants did not provide consent.

Figure 2.3:   **Total number of participants screened and enrolled in the FluMum cohort study (by site of enrolment) and self-reported receipt of influenza vaccine during pregnancy, Australia (2012-2014).**
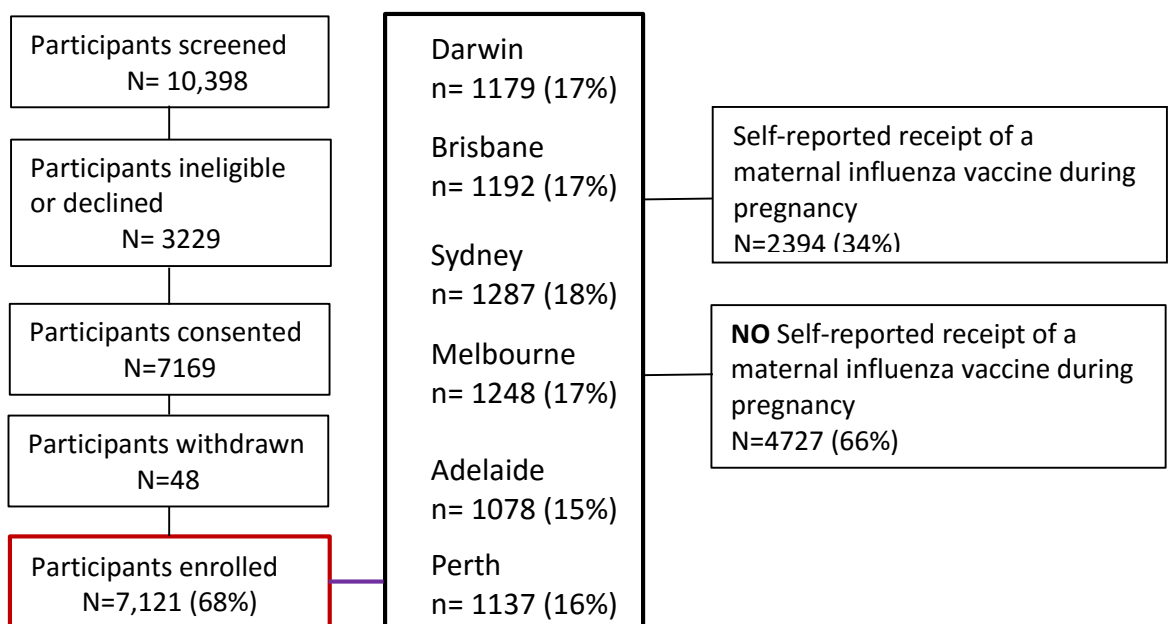
Of the 7,121 mother-infant pairs who were enrolled in the study, the mean maternal age was 31.7 years and 203 (3%) of mothers were of Aboriginal and/or Torres Strait Islander origin. The mean gestation at birth was 38.7 weeks, mean birthweight was 3332 grams whilst 52% of infants were male. The ratio of maternally vaccinated:unvaccinated participants was 1:1.9 (34% v 66%). There were:

- 4,302 (60%) women recruited through public hospitals, 1,986 (28%) through private hospitals and 819 (12%) recruited outside the hospital system or where the place of birth of the infant was not specified.
    - Amongst the vaccinated group, the distributions were 58% public, 33% private, 9% other.
    - Amongst the unvaccinated group, the distributions were 62% public, 25% private, 13% other

Baseline maternal characteristics by vaccination status

Maternal characteristics at enrolment were similar between the vaccinated and unvaccinated cohorts (Table 2.4). There were a range of variables that showed statistically significant results as summarised below but the differences were neither substantive nor clinically meaningful. In the vaccinated group, 53% of women reported educational qualifications as having a degree or higher. In the unvaccinated group, this was 45%.

Maternal co-morbidities and risk factors

With regards to maternal co-morbidities and risk factors for influenza infection, there were no statistically significant or clinically meaningful results between the two groups apart from diabetes and the variable 'ANY co-morbidity/risk factor'(Table 2.5). Women with any form of diabetes were 20% more likely to report receiving a maternal influenza vaccination in pregnancy compared to women without diabetes (RR 1.2, 95% CI 1.06-1.46, p 0.006). Women reporting 'ANY co-morbidity or risk factor' were 10% more likely to have received a maternal influenza vaccination compared to mothers without any co-morbidity or risk factor (RR 1.1, 95% CI 1.04-1.25, p 0.007).

Table 2.4: **Baseline characteristics of the FluMum study participants, by self-reported influenza vaccine in pregnancy status, Australia (2012-2014)**

Characteristics	Vaccinated N (34%)	Unvaccinated N (66%)	Total N=7121	Relative Risk (RR) 95% CI	p value	Difference 95% CI
Maternal **age (mean, in years)**	32.1	31.5	31.7	NA	**0.000**	**- 0.7** -0.92,-0.40
Mothers who identify as **Aboriginal and or Torres Strait Islander**	75/2393 (3%)	128/4720 (3%)	203/7118 (3%)	RR 1.16 0.87,1.53	0.31	0.4% -0.42%,1.26%
Gestation (mean, in weeks) when 1st received antenatal care	8.2	8.8	8.6	NA	**0.000**	**0.6** 0.25,0.88
Self-reported maternal **respiratory illness** during pregnancy	426/2393 (18%)	743/4724 (16%)	1169/7117 (16%)	**RR 1.1** 1.02,1.3	**0.03**	**2%** 0.22%,3.92%
Self-reported maternal **smoking** in pregnancy	142/2392 (6%)	383/4726 (8%)	524/7118 (7%)	**RR 0.73** 0.69,0.92	**0.001**	**-2%** -3.40%,-0.95%
Exposure to **indoor tobacco** smoke during pregnancy	57/2392 (2%)	152/4712 (3%)	209/7104 (3%)	**RR 0.74** 0.55,1.00	**0.047**	**-0.8%** -1.63%,-0.05%
Exposure to **household tobacco** smoke during pregnancy	403/2393 (17%)	1023/4721 (22%)	1426/7114 (20%)	**RR 0.78** 0.70,0.86	**0.000**	**-5%** -6.73%, -2.92%
English primary language spoken at home	1906/2308 (83%)	3692/4575 (81%)	5602/6883 (81%)	RR 1.02 0.99,1.05	0.07	1.8% -0.14,%, 3.70%
Lives with other children who attend **daycare/preschool** (excludes the birth infant)	577/2391 (24%)	1210/4721 (26%)	1784/7112 (25%)	RR 0.94 0.86,1.02	0.16	-1.5% -3.65%, -0.58%

Note: denominators differ due to missing data, RR refers to the relative risk of the vaccinated cohort compared with the unvaccinated cohort

Table 2.5:   Co-morbidities of 7121 FluMum study participant mothers, by self-reported maternal influenza vaccine in pregnancy status, Australia, 2012-2014.

Characteristics	Vaccinated N (%)	Unvaccinated N (%)	RR 95% CI	Difference 95% CI	p-value
Heart disease	21/2394 (0.9%)	32/4721 (0.7%)	RR 1.3 0.75,2.24	0.2% -0.24%, 0.64%	0.62
Hypertension*	271/2394 (11%)	473/4721 (10%)	RR 1.1 0.98,1.30	1.3% -0.23%, 2.83%	0.09
Severe pneumonia requiring hospn.	45/2392 (1.8%)	72/4720 (1.5%)	RR 1.2 0.85,1.78	0.4% -0.29%, 1.00%	0.27
Chronic respiratory condition†	50/2391 (2%)	81/4721 (2%)	RR 1.2 0.86, 1.73	0.4% -0.31%, 1.06%	0.27
Immunosuppressive condition‡	20/2392 (1%)	33/4721 (1%)	RR 1.2 0.69,2.08	0.1% -0.30%, 0.57%	0.53
Cancer requiring treatment	14/2389 (1%)	39/4719 (1%)	RR 0.8 0.47,1.44	-0.2% -0.59%, 0.27%	0.48
Diabetes mellitus§	231/2393 (10%)	366/4721 (8%)	**RR 1.2** 1.06,1.46	**2%** 0.49%, 3.31%	**0.006**
Regular use of immune medication	38/2392 (1.6%)	48/4720 (1.0%)	RR 1.6 1.02,2.38	0.6% -0.01%,1.15%	0.11
ANY co-morbidity/risk factor‖	558/2393 (23%)	969/4721 (21%)	**RR 1.1** 1.04,1.25	**3%** 0.74%, 4.84%	**0.007**

Note: denominators differ due to missing data, RR refers to the relative risk of the vaccinated cohort compared with the unvaccinated cohort

* Including essential hypertension, gestational hypertension and pre- eclampsia

† Including emphysema or severe asthma requiring frequent hospital visits

‡ Including HIV/AIDS

§ Including type 1, type 2 and gestational diabetes

‖ Results of pooled risk factors and comorbidities

Infant characteristics

Sex and Indigenous status

There were no differences in either the sex of the infant or of the Indigenous status of the infant between the vaccinated and unvaccinated cohort (Table 2.6).

Table 2.6:   Sex and Indigenous status of 7121 infants born to participants enrolled in the FluMum study, by self-reported maternal influenza vaccine in pregnancy status, Australia, 2012-2014.

Characteristics	Vaccinated N (%)	Unvaccinated N (%)	RR 95% CI	Difference	p-value
Sex (n, %) **Male**	1249/2391 (52%)	2447/4723 (52%)	RR 0.99 0.94-1.04	0	0.73
Indigenous * **(n, %)**	100/2393 (4%)	194/4717 (4%)	RR 1.02 0.80- 1.29	0	0.89

* Infants who have been identified by a parent as being Aboriginal and/or Torres Strait Islander.

Trimester of receipt of influenza vaccination

There were 1009 mothers for whom a date of receipt of an influenza vaccination during their pregnancy had been ascertained. Of these, 142 (14%) received the influenza vaccine during the first trimester, 471 (47%) in the second trimester and 396 (39%) in the third trimester (Table 2.7).

Table 2.7:   Breakdown of maternal influenza vaccine by trimester of pregnancy

Trimester mother received vaccination	N=1009
1st trimester	142 (14%)
2nd trimester	471 (47%)
3rd trimester	396 (39%)

Mothers who received a maternal influenza vaccination in their first trimester gave birth to infants at a mean of 38.3 weeks gestation, compared to a mean of 38.7 weeks in mothers who were not vaccinated. Although this is a statistically significant difference (0.4 weeks, 95%CI 0.01 to 0.80 weeks, p 0.04), the difference is minimal and not clinically relevant, even at the upper confidence limit of 0.8 weeks given the mean

gestation under those circumstances would still be considered as full-term. The mean birthweight in grams was no different between the women vaccinated during the first trimester compared with those who were not vaccinated.

Table 2.8: **Birth outcomes of mothers who received an influenza vaccine in their 1st trimester of pregnancy compared to mothers who did not receive an influenza vaccine in pregnancy, Australia 2012-2014.**

Characteristics	Vaccinated 1st trim. (3%)	Unvaccinated (97%)	Difference 95% CI	p value
Gestation (mean, in weeks) at birth of infant	38.3	38.7	0.4 0.01,0.80	**0.04**
Birthweight of infant (mean, in grams)	3258	3336	78 grams -36.0,191.0	0.18

Weeks in gestation and birthweight

There were no statistically significant differences between vaccinated and unvaccinated mothers in relation to weeks' gestation at birth of the infant and infant birthweights (Table 2.9). Gestation in weeks at birth of the infant was 38.7 for the cohort as a whole and for both the vaccinated and unvaccinated group (Table 2.9). There was an 11 grams difference in birthweight between infants born to mothers in the vaccinated group (3325 grams) compared to infants born to mothers in the unvaccinated group (3336 grams, p-value 0.52).

Table 2.9: **Birth outcomes of 7121 FluMum study participants by self-reported (SR) maternal influenza vaccine in pregnancy status, Australia (2012-2014).**

Study outcomes	Vaccinated N (%)	Unvaccinated N (%)	RR & 95% CI	Difference 95% CI	P-value
Gestation at birth (mean, in weeks)	38.7	38.7		0.04 -0.07,0.16	0.43
Preterm infants[*] (n, %)	436/2391 (18%)	751/4712 (16%)	**1.14** 1.03-1.27	2.3% 0.43,4.16	**0.014**
Very premature infants[†] (n, %)	69/2019 (3%)	128/4086 (3%)	1.09 0.82-1.45	0.3% -0.67,1.24	0.55
Extremely premature infants[‡] (n, %)	11/1961 (0.6%)	23/3981 (0.6%)	0.97 0.47-2.00	-0.02 -0.42,0.39	0.97
Birthweight of infant (mean, in grams)	3325	3336		10.5 -21.68,42.78	0.52
Normal infant birthweight (2500g-3999g), (n=, %)	1977/2382 (83%)	3909/4699 (83%)	0.98 0.98-1.02	-0.19% -2.03,1.66	0.84
Low birthweight infants[§] (n, %)	158/2393 (6.6%)	305/4721 (6.5%)	1.02 0.85-1.23	0.14% -1.08,1.40	0.82
Very low birthweight infants [‖] (n, %)	14/2381 (0.6%)	35/4693 (0.7%)	0.79 0.43-1.46	-0.16% -0.55,0.24	0.45
Extremely low birthweight infants[¶](n, %)	1/2380 (0.04%)	11/4693 (0.2%)	0.18 0.02-1.39	-0.19% -0.35,-0.33	0.06
Large for gestational age infants[**] (n=, %)	253/2381 (11%)	494/4199 (11%)	1.01 0.87-1.16	0.10% -1.42,1.62	0.90

Note: denominators differ due to missing data
* Infants born before 37 completed weeks' gestation
† Infants born before 35 completed weeks' gestation
‡ Infants born before 30 completed weeks' gestation
§ Infants weighing less than 2500 grams at birth
‖ Infants weighing less than 1500 grams at birth
¶ Infants weighing less than 1000 grams at birth
** Infants weighing greater than 4000 grams at birth

Infants born to vaccinated mothers were 14% more likely to be born preterm (RR 1.14, 95% CI 1.03-1.27, p-value 0.014, 18% versus 16%). Most importantly though, from a clinical perspective (Table 2.9), there were no observed differences between the vaccinated and unvaccinated cohorts with respect to very premature births (3% in each group) or extremely premature births (0.6% in each group). There were no observed differences with regards to birthweight.

Discussion

In this study of 7,121 mother-infant pairs from multiple sites across Australia over three consecutive years, there was no evidence of clinically meaningful differences in birth outcomes (birthweight or gestation) for women who received an influenza vaccination during pregnancy compared with those who were not vaccinated in pregnancy (Table 2.9). In addition, there was no evidence to suggest any increased risk of having an adverse birth outcome from receiving an influenza vaccine during the first trimester when compared with receiving the vaccine during the second or third trimester of pregnancy. In this large sample size, we did find that infants born to vaccinated mothers were 14% more likely to have a preterm birth than infants born to unvaccinated mothers (RR 1.14, 95% CI 1.03-1.27, p-0.014). Whilst the difference was statistically significant, the absolute difference in the proportion of preterm infants between the two groups was only 2% (18% amongst maternally vaccinated versus 16% amongst maternally unvaccinated). This difference was not of major clinical importance given these infants were neither extremely premature nor very premature (two serious categories of prematurity for which there were no differences between the vaccinated and unvaccinated cohort).

Others have found evidence suggesting receipt of an influenza vaccination during pregnancy reduces the risk of preterm births and reduces the risk of having a low birth weight infant.[11,12,15,17] Legge et al., found infants with low birthweights occurred less in the vaccinated group (adjusted odds ratio [aOR] 0.73, 95% CI 0.56–0.95) compared to the unvaccinated group, and preterm births occurred less in the vaccinated group compared to the unvaccinated group (adjusted odds ratio 0.75, 95% CI 0.60–0.94).[13] A similar study by Sheffield et al.,[12] showed no differences in mean birthweights

between the vaccinated and unvaccinated group and found less preterm births in the vaccinated group (5%) compared to the unvaccinated group (6%) with a p-value of 0.004.

Study outcomes

Preterm births and infant birthweights

Infants who are born prematurely are known to be at much higher risk of adverse neonatal outcomes than those infants who are born at term.[20] These outcomes can include long term physical and developmental difficulties as well as higher risks of acquiring co-morbidities.[21]

The results of my study are reassuring with regards to the safety and birth outcomes for gestation. There was no evidence to suggest that receiving an influenza vaccine in pregnancy was associated with preterm births. Mothers in the vaccinated and unvaccinated group both gave birth at 38.7 weeks gestation which was also the recorded mean duration of pregnancy for Australian women as a whole in 2014.[21]

Infant birthweight is an important indicator of health.[20] The mean birthweight of all live born infants in the Australian population in 2012 was 3367 grams [21] which is similar to the mean birthweight in grams of infants in our study population as a whole which was 3331 grams. There was only 11 grams difference in birthweight between babies born in the vaccinated group compared to babies born in the unvaccinated group. This suggests there is no evidence receiving an influenza vaccine in pregnancy is related to low birthweight of infants or infants born large for gestational age. The proportion of infants born within the normal weight range of 2500g-4000g in my study for the vaccinated and unvaccinated group was 85% for both groups. This is the same proportion of infants born within the normal weight range for the Australian population for 2012.[20]

On closer examination of infant's birthweights, there were no differences between the vaccinated and unvaccinated groups in relation to proportions of infants who were born of low birthweight, very low birth birthweight, extremely low birth weight or

large for gestational age. The proportions of the infants in these categories for the vaccinated and unvaccinated groups were the same as those for infants in the Australian population in 2012.[21] These data are encouraging regarding the support of receiving an influenza vaccine during any stage of pregnancy and are substantiated by safety studies presented in overseas literature.[11,12]

There were minor differences in demographics between the unvaccinated and vaccinated group, with many of the statistically significant differences being very small in real terms, a reflection of the large sample size. The mean age in years of participants was 31.7 which was similar to the mean age in years of women giving birth in Australia in 2012.[21] The proportion of Aboriginal and Torres Strait Islander women in the total cohort was 3%. This was slightly lower than the national data, of which 4% of births in 2012 were to Aboriginal and Torres Strait Islander women;[20] likely a reflection of study participants recruited from large inner city hospitals from the major capital cities.

Maternal co-morbidities and risk factors for influenza infection

Influenza vaccination is recommended for pregnant women who will be pregnant during the influenza season.[8] Other potential at-risk groups that should receive an influenza vaccination are those with pre-existing co-morbidities and those who are at risk of acquiring influenza infection.

In our study, we found no statistically significant or clinically important differences in the proportions of mothers with co-morbidities or risk factors for acquiring influenza infection when comparing the vaccinated and unvaccinated groups. This was surprising considering current recommendations in Australia specifically target these high-risk women for annual influenza vaccination (regardless of their pregnancy status).[8]

Pregnant women with diabetes showed a statistically significant result in the analysis (RR 1.2, 95% CI 1.06-1.46, p-0.006). The difference between the groups was small at 2%, and this finding could be a consequence of a large sample size, however considering the high public health importance and clinical significance of diabetes in

pregnancy these results should be reflective rather than dismissive. Overseas literature[5,12] however found no statistically significant differences in preterm births or low birthweights between the vaccinated and unvaccinated groups of mothers who had diabetes in pregnancy.

Trimester of pregnancy received influenza vaccine

Where a date of influenza vaccination in pregnancy was ascertained, most participants were vaccinated during the second and third trimesters of pregnancy (86%) compared to the first trimester (14%). Our data found no differences in birth outcomes between mothers who received an influenza vaccine during the first trimester of pregnancy compared to mothers who were confirmed as having received an influenza vaccine during the second or third trimesters of pregnancy. These results suggest it is safe to receive an influenza vaccine at any stage during pregnancy which is supported by other emerging overseas literature.[12]

Strengths

The strength of the project lies in the design of the original FluMum prospective cohort study. Although the study population is not a random sample, all eligible participants in this nested cohort arise from the original FluMum study where the exposure (maternal vaccination status) and outcomes of interest (birth weight and gestation at birth) were not known by the investigators at the time of recruitment and unlikely to have been a factor in participant consent since the primary outcome of interest for the overarching FluMum study was laboratory confirmed influenza in infancy (which had not yet occurred). Data quality was of a high standard with minimal missing data for variables. As a retrospective cohort, internal validity is provided by between cohort comparisons (vaccinated versus unvaccinated). The large sample size does provide precision around the estimates of effect. As a non-random sample of women giving birth in urban centres, who are predominantly first language English speakers, there are potential biases that may limit generalisability of the findings. Of note however, the study sample had very similar mean birthweight and gestational age at birth almost identical to published Australian data on perinatal outcomes as discussed in selection bias below.

There is a lack of rural and remote representativeness of pregnant women in the study population as all participating sites are major Australian capital cities. Generalisability of these results to the wider population should therefore be treated with caution. Influenza vaccine uptake by pregnant Aboriginal and Torres Strait Islander women in my study was 37% which is consistent with the overall vaccine uptake in the cohort. It must be noted that apart from the Darwin site, participant numbers in this study were small for Aboriginal and Torres Strait Islander women and therefore results for these women may not be reflected in the birth outcomes of this study.

We know that pregnant women who present for antenatal care before 16 weeks gestation for their first pregnancy have better birth outcomes than pregnant women who present later.[22] My study shows an overall sample of pregnant women who attended antenatal care early at 8.4 weeks. This early presentation for antenatal care is reflective of pregnant women from the Australian population as a whole.[20]

Limitations

Selection bias

The recruitment selection strategy for this nested cohort study was pre-determined by the overarching FluMum study, which is a non-random sample.[1] Whereas the original study recruited participants before their outcome of interest was known (laboratory confirmed influenza in infants in the first 6 months of life), the nested cohort is effectively a retrospective cohort design since the primary outcomes have already occurred at the time of recruitment. As such, we cannot know whether there are any differences in non-responders compared to those who consented to be in this study. Apart from place of birth of the infant; private versus public hospital, we cannot know whether eligible participants who declined consent to be in the FluMum cohort study have certain demographic, behavioural and health characteristics which may be potentially quite different to the consenting cohort.

Women were required to be >17 years old to be considered eligible to consent to this study. This excluded a large demographic of young mothers from being in the cohort.

This in turn made it more likely that a larger proportion of Aboriginal and Torres Strait Islander mothers were excluded from being in the study as these women tend to have their first child at a younger age than Non-Indigenous women.[20] Traditionally Aboriginal and Torres Strait Islander women have much higher rates of prematurity and lower birthweight infants than non-Indigenous women,[21] so it is possible the birth outcomes of these women will not be reflected in the birth outcomes of my study.

Women needed to be able to speak fluent English to be eligible to consent to this study. This excluded a large urban migrant population who may not speak fluent English from being part of the cohort. Again this requirement also potentially excluded some Aboriginal and Torres Strait Islander women whose first language is not English. As a result we will not know whether these groups of women are more or less likely to access or be offered maternal influenza vaccination in pregnancy and if they are offered a vaccine whether they would be more or less likely to accept the offer of vaccination. We also will not know if these subgroups have or have not received an influenza vaccine during pregnancy and whether there are any subsequent differences in birth outcomes between these groups. However, a study by Sheffield et al.,[12] examined birthweights and preterm births in vaccinated and unvaccinated groups of pregnant women that included women; under 17 years of age as well as non-English speaking and those in minority groups. Their results remained consistent with the results from this study showing no differences in preterm births or birthweights between vaccinated and unvaccinated pregnant women.

Women must have birthed a live baby to be eligible to be in this study. This prevented us from knowing an element of safety around maternal vaccination in pregnancy related to birth outcomes as we have no data on stillbirths or late spontaneous abortions. There are however, encouraging data from a systematic review looking at stillbirths and spontaneous abortions that showed there were no differences between women who had an influenza vaccine in pregnancy compared to women who did not.[14]

Although there was a statistically significant difference in the analysis of maternal age in years at birth of the infant between vaccinated mothers compared to unvaccinated mothers in pregnancy, this difference was only six months and unlikely to have clinical implications for public health practice.

Minimising selection bias

There is a clearly defined eligibility criterion for the original FluMum cohort study as well as a well-defined protocol as to how data are to be collected.[1]

A feature of the original cohort study attempted to recruit a mix of participants from public and private hospitals. This is not reflected in these data as there are twice as many participants recruited from public hospitals than private hospitals.

Participant loss to follow up within this nested study was minimised by nature of the study design. Any loss to follow up will have already occurred in the original prospective cohort prior to analysis. The analysis plan for the nested cohort study focused on within cohort comparisons. Collecting demographic and risk factor data enabled an assessment of influences between the vaccinated and unvaccinated cohorts. A review of published Australian data on perinatal outcomes from the AIHW national perinatal statistics data was used to compare national demographic and risk factor data with the demographic and risk factor data from my study. This was to identify whether there could be potential biases such as volunteer or in this case 'healthy vaccinee effect' bias.[20]

Potential measurement error for study exposure and outcome factors

Misclassification of exposure is possible if some participants were labelled as having had an influenza vaccine in pregnancy (exposed) when they did not (unexposed), and vice versa.

This was a consequence of using self-reporting of receipt of an influenza vaccination during pregnancy. Validation studies on self-reporting of receiving an influenza vaccine by age group demonstrate high reliability,[18] however data on self-reporting in

pregnancy is scant. Misclassification of outcome is also possible if some participants were labelled as having had an infant born prematurely or of low birth weight incorrectly however validation studies conducted on self-reporting of birth outcomes by mothers,[18] show a high reliability so this is unlikely.

There is potential measurement bias for the study outcome gestation in weeks at birth of the infant. Data for this variable were self-reported by the mother and subsequently collected by the researcher and then entered into the database. Other studies state the use of self-reported gestation in weeks by the mother in their research.[13] These are supported by the same validation study above demonstrating high reliability of maternal self-reporting of gestation at birth of the infant and infant birthweights.[17] Other literature has not stated how gestation was calculated in their studies.[11,12]

Minimising measurement error for study exposure and outcome factors

The original FluMum study questionnaire is a detailed form where trained health researchers collected information. It was piloted by research staff at each site prior to the commencement of the study in 2012. There were revisions to the questionnaire over the course of the study however this would not have influenced data used in this analysis. Data entry error is inevitable, though coding the Stata .do file in preparation for data analysis enabled cross checking of questions such as gestation at birth of infants to determine whether participants were potentially misclassified or not. Data were examined for logic and consistency. Illogical outliers were individually checked at the point of data cleaning for dates of birth of infant and where available LNMP.

Effort was also made to reduce measurement bias in the study outcome variable 'gestation in weeks at birth of the infant'. Where data were available, gestations in weeks were calculated if the date of the LNMP was collected. Although dates, birthweights of infants and gestations at birth of the infants were self-reported by the mother, again validation studies on self-reporting with regards to these birth outcomes have verified moderate to high reliability of the self-reported results when compared with medical records.[18]

Public Health Implications

Maternal influenza vaccine uptake is a public health policy initiative that has been advocated for more than a decade without any systematic initiatives to monitor implementation or birth outcomes.[1] Providing further evidence around the safety of receiving a vaccine during pregnancy, particularly infant birthweights and preterm births may help increase uptake of the vaccine. This may reduce the morbidity and mortality that results from influenza infection when it occurs during pregnancy. We know historically that during previous influenza pandemics, 50% of the deaths that occur among women of child-bearing age are amongst pregnant women.[2,16]

Current policy and Recommendations

In Australia, the influenza vaccine is recommended for all pregnant women who will be pregnant during the flu season.[8]

The primary focus is preventing serious consequences for the mother from influenza infection during pregnancy.[23] Women who are at higher risk of acquiring influenza infection due to reduced immunity or due to the presence of co-morbidities are targeted for immunisation with the influenza vaccine.[15,2,22]

Conclusion

The birth outcomes results arising from this first Australian study are reassuring. In relation to the safety of receiving a maternal influenza vaccination during pregnancy, based on these findings, health care providers can confidently promote the influenza vaccine for all pregnant women and reassure them and their families regarding the safety of receiving the vaccine during any stage in pregnancy. Finally it can be deemed appropriate to offer the vaccine to all pregnant women in accordance with the current recommendations in Australia.

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Appendix 2.1.   FluMum study participant questionnaire

1. Participant entry into FluMum nested study

Note:
  i.   This form is an excerpt from the original FluMum cohort study questionnaire (which was developed by Ross Andrews) showing questions that I have used in the nested cohort study.
  Question numbers are based on the original form and it will appear some are missing or out of order , however this is intentional as it will assist with data analysis in stata (where the do file is written based on question numbers labelled in the original form).
  *I will not be able to see any of the participant's identifiable information in the nested dataset therefore I have excluded the variables 'Contact details' and 'Baby's name' from this questionnaire.
  ii.   All dates are dd/MMM/yyyy format, ie 02/FEB/2011
  iii.   Yes/No questions may also include "Unk", which = Unknown/Unsure/Don't know

1.02   Informed consent obtained from the participant [Consent]

Must be seen by YOU (signed by the person AND by a Team member) ↳…

No ☐0   Yes ☐1   If **No** do not proceed
↳ STOP

1.03   Sufficient verbal English demonstrated in consent process to allow questionnaire completion [English1] ↳…

No ☐0   Yes ☐1   If **No** do not proceed
↳ STOP

1.04   Interview date for participant questionnaire
[DateSEQ]

dd/mmm/yyyy   /   /
↳…

1.05   Interview being conducted within the specified window period (38wks gest - 8 wks post delivery)? [FUWindow] ↳…

Note:Although the protocol allows enrolment from 38wks gest, sites are now focussing on postnatal recruitment

No ☐0   Yes ☐1   Unk ☐9   If **No** do not proceed
↳ STOP

2. Confirmation of eligibility
Shaded boxes indicate mum is ineligible – if so, do not include in study

2.03   Could you please tell me your date of birth? [MaternalDOB]:

dd/mmm/yyyy   /   /   Dcl ☐ 10
↳…

2.04   Confirm participant is aged 17 years or more at enrolment? [Age17]: ↳…

No ☐0   Yes ☐1   If **No** do not proceed
↳ STOP

4. Mum's health

4.02   How many weeks pregnant were you when you first started receiving antenatal care during your pregnancy? [Antenatal] ↳…
(enter 0 if not attended any antenatal care)

☐☐ weeks   Unk ☐99   Dcl ☐ 100

4.06   During your pregnancy, did you ever have a respiratory illness with symptoms like fever, chills, cough, aches and pains, that caused you to see a doctor? [MatILI] ↳…

No ☐0   Yes ☐1   Unk ☐9   Dcl ☐ 10
↳7.01   ↳7.01

Team Member Initial: |__.__| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

5. Episodes of respiratory illness during your pregnancy that caused you to see a doctor

Thinking now about the 1st episode of respiratory illness during your pregnancy that caused you to see a doctor, can you tell me …

5.01 **Tests done** [Mat1Test]

No ☐0	Blood ☐1	Nose ☐2	Throat ☐3	Unk ☐9	Dcl ☐10
↳5.06				↳5.06	↳5.06

5.04 How many weeks pregnant were you? [Mat1FluWks]
↳… |__|__| weeks   Unk ☐99   Dcl ☐ 100

5.06 Did you have a **2nd episode** of respiratory illness in pregnancy that caused you to see a doctor? [Mat2ILI]
↳…   No ☐0   Yes ☐1
                                                                                              ↳7.01

5.07 **Tests done** [Mat2Test]

No ☐0	Blood ☐1	Nose ☐2	Throat ☐3	Unk ☐9	Dcl ☐10
↳6.01				↳6.01	↳6.01

5.10 How many weeks pregnant were you? [Mat2FluWks]
↳… |__|__| weeks   Unk ☐99   Dcl ☐ 100

Team Member Initial: |__.__| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

6. Further episodes of respiratory illness during your pregnancy that caused you to see a doctor

6.01 Did you have a **3rd episode** of respiratory illness in pregnancy that caused you to see a doctor? [Mat3ILI]

No □0 Yes □1

↳...

↳7.01

6.02 Tests done [Mat3Test]

No	Blood	Nose	Throat	Unk	Dcl
□0	□1	□2	□3	□9	□10
↳7.01				↳7.01	↳7.01

6.05 How many weeks pregnant were you? [Mat3FluWks]

↳...

|__|__| weeks Unk □99 Dcl □ 100

6.07 Did you have a **4th episode** of respiratory illness in pregnancy that caused you to see a doctor? [Mat4ILI]

No □0 Yes □1

↳...

↳7.01

6.08 Tests done [Mat4Test]

No	Blood	Nose	Throat	Unk	Dcl
□0	□1	□2	□3	□9	□10
↳7.01				↳7.01	↳7.01

6.11 How many weeks pregnant were you? [Mat4FluWks]

↳...

|__|__| weeks Unk □99 Dcl □ 100

Team Member Initial: |__.__| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

		No	Yes	Unk	Dcl
7.09	Did you get a **flu vaccine** during this pregnancy? [FluvaxPreg]	☐0	☐1	☐9	☐10
	If NO or Unknown go to 9.01	↳...			
		↳9.01		↳9.01	↳9.01

10. Flu vaccine during the 12 months BEFORE you became pregnant

		No	Yes	Unk	Dcl
10.01	Some people have had the flu vaccine BEFORE they got pregnant. Thinking about the 12 months before you became pregnant, did you get a flu vaccine during that time? [Fluvax12mths]	☐0	☐1	☐9	☐10
	If No or Unknown go to 11.01	↳...			

11. More vaccine history questions

		No	Yes	Unk	Dcl
11.01	We have already asked about your pregnancy and the 12 months prior to becoming pregnant, other than these times, have you EVER had a flu vaccine? [FluvaxEver] ↳...	☐0	☐1	☐9	☐10
		↳11.06	↳11.06		↳11.06

PART B – 12. Birth of your baby

					Dcl
12.01	What date did you deliver (give birth to your baby or baby)? [DeliveryDate]: dd/mmm/yyyy ↳...	/	/		☐10

12.03			Study site [Site]	Dwn ☐1	Brb ☐2	Syd ☐3	Mel ☐4	Adl ☐5	Per ☐6
	(If Darwin, go to 12.05 = do NOT stop) ↳...			↳ 12.05					

12.04 Birth month [Bmth]

Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐ 10	☐ 11	☐ 12
↳ STOP									↳ STOP	↳ STOP	↳ STOP

12.05	Live birth/s? [LiveBirth]	No ☐0	Yes ☐1	If **No** do not proceed
	↳...			

				weeks	Unk	Dcl
12.07	How many weeks pregnant were you at the time of delivery? [Gestation] ↳...			weeks	☐ 99	☐ 100

					Unk	Dcl
12.08	What was the date of your last menstrual period prior to your pregnancy? [LMPdate]: dd/mmm/yyyy ↳...	/	/		☐9	☐10
					↳ 12.10	↳ 12.10

Team Member Initial: |__.__| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

14.03   **Birthweight (g)** [B1Wgt]   14.04   **Gender** [B1Sex] note: Ind=Indeterminate

↳... |___|___|___.___| ↳...   Ind   M   F   Dcl

grams   Unk   Dcl   □0   □1   □2   □
                      □9   □   10
                      9   10

14.06   **Live Birth** (cross checking with Q12.05)

[B1Live]
                      No   Yes   Dcl
↳...   □0   □1   □
                            10
↳17.01

14.08   Since birth, has your baby been diagnosed with a   No   Yes   Unk   Dcl
        condition that suppresses the immune system?   □0   □1   □9   □
        [B1Immune]   10
                                                                  ↳14.10   ↳   ↳
                                                                          14.10 14.10

14.09 | If yes, what is the name of that condition? [B1ImmuneName] | Unk   Dcl
        | | □9   □
        | | 10

14.10   Has your baby been given any steroids or   No   Yes   Unk   Dcl
        medications since birth that suppress the immune   □0   □1   □9   □
        system? [B1Steroids]   10
                                                                  ↳14.12   ↳   ↳
                                                                          14.12 14.12

14.11 | If yes, why was he/she given these medications? [B1Steroid_reason] | Unk   Dcl
        | | □9   □
        | | 10

14.12   Has your baby been diagnosed with any illnesses   No   Yes   Unk   Dcl
        requiring medical follow-up (on a regular basis) or   □0   □1   □9   □
        hospitalisations?   10
        [B1HighRisk]   ↳17.01   ↳   ↳
                                                                          17.01 17.01

14.13 | If yes, what is the name of that condition? [B1HighRiskName] | Unk   Dcl
        | | □9   □
        | | 10

Team Member Initial: |___.___| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

17. Some general questions about your own health

Note: 17.01-17.11 list medical conditions pre-disposing to severe influenza as specified in the Immunisation Handbook, 10th edition

Have you EVER been told by a doctor that you have had any of the following conditions

Ask each one

		No	Yes	Dcl
17.01	…Heart disease [Heart]	☐0	☐1	☐10
17.02	…High blood pressure or hypertension (including gestational hypertension and pre eclampsia) [Hypertension]	☐0	☐1	☐10
17.03	…Severe pneumonia (requiring hospitalisation) [Pneumonia]	☐0	☐1	☐10
17.04	…Chronic respiratory condition (including emphysema or severe asthma requiring frequent hospital visits) [Bronchitis]	☐0	☐1	☐10
17.05	…Immunosuppressive condition (inc HIV/AIDS) [Immune]	☐0	☐1	☐10

During your pregnancy or the 12months before you were pregnant, have you been told by a doctor that you have had any of the following conditions

Ask each one

		No	Yes	Dcl
17.09	…Cancer (requiring treatment) [Cancer]	☐0	☐1	☐10
17.10	… Diabetes (type 1 or 2, including gestational diabetes) requiring hospitalisation or medical follow-up [Diabetespreg]	☐0	☐1	☐10
17.11	Regular use of immunosuppressive medications [ImmuneMedspreg]	☐0	☐1	☐10

			Dcl
17.12	How many cigarettes do you usually smoke in a day? [Smokes] ↳…	☐☐ cigs	☐

900

		No	Yes	Dcl
17.13	Did you smoke any cigarettes during your most recent pregnancy? [PregSmoker] (includes before you knew you were pregnant) ↳…	☐0	☐1	☐10

Team Member Initial: |__.__| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

18. Now to finish with some general questions

18.01 Are you of Aboriginal or Torres Strait Islander origin? [ATSIMum]
↳...

No ☐0   AB ☐1   TSI ☐2   Both ☐3   Dcl ☐ 10

18.02 Is your baby of Aboriginal or Torres Strait Islander origin? [ATSIBaby]   ↳...

No ☐0   AB ☐1   TSI ☐2   Both ☐3   Dcl ☐ 10

18.03 Were you born in Australia? [AustralianBorn]   ↳...

No ☐0   Yes ☐1   Dcl ☐ 10
↳18.06

18.04 Country of birth? [BirthCountry]

Dcl ☐ 10

18.06 Is English the main language you usually speak at home?
[English2]   ↳...

No ☐0   Yes ☐1   Dcl ☐ 10
↳18.08

18.07 What is the main language you speak at home? [Language]

Dcl ☐ 10
↳18.08

18.08 How many people usually live at your house? [Occupancy]
counting the new baby (babies)   ↳...

| | | Unk ☐ 99 | Dcl ☐ 100 |

18.14 Do any of the children who usually live at your house also attend child-care or day-care? [DayCare]
↳...

No ☐0   Yes ☐1   Dcl ☐ 10

18.15 How many of the people who live at your house, smoke cigarettes? [HouseholdSmoker]   ↳...

| | | Unk ☐ 99 | Dcl ☐ 100 |

18.16 Were you regularly exposed to indoor tobacco smoke during your pregnancy, including before you found out you were pregnant? [IndoorSmoke]

No ☐0   Yes ☐1   Dcl ☐ 10

Team Member Initial: |__.__| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

19. Last page of the Study Entry Questionnaire

19.01   Which of the following describes the highest
educational qualification you have obtained
[Education]

Did not finish high
school   Dcl
☐₁   ☐
                               10

High School
☐₂

Certificate
☐₃

Diploma
☐₄

Degree
☐₅

Postgraduate degree
☐₆

Team Member Initial: |__.__| Date (dd/mmm/yyyy): __ __ / __ __ __ / __ __ __ __

Appendix 2.2.   Stata do-file for FluMum data analysis

```
*cr_FluMum_epiproject_Dec2014.do was written by Lisa McHugh
*last updated 15Nov 2015 and last run 15November 2015.
*This do file creates a FluMum nested dataset called
FluMum_epiproject_Dec2014.dta
*based on Flumum_all.xls export from FileMaker Pro
*The do file labels, cleans and, where necessary,
*recodes the data set in preparation for data analysis.

* Change working directory in STATA, for me that's
*"C:\MAE for uni\FluMum epi project\Data analysis\Do files\FluMum nested study
export 12Dec2014.csv", case
capture log close
version 12.1
clear
set more off
log using cr_FluMum_epiproject_Dec2014.log,replace

*******************************************************************************
****
** 1. FluMum_all.xlsx -> FluMum_all.dta
*******************************************************************************
****
*import excel "S:\QCMRI-RiOAR\FluMum Study National\MAE for uni\FluMum epi
project\Data analysis\Do files\FluMum nested study dataset 20Nov2014.xls",
firstrow
*insheet using "C:\MAE for uni\FluMum epi project\Data analysis\Do
files\FluMum nested study export 12Dec2014.csv", case
*******************************************************************************
****
**       - code below could be run off server to create FluMum_nested.dta
**       - this can then be re-run off a future export for any subsequently
cleaned data meeting future requirements
**         (would just need an extra command like keep if DeliveryDate > xxx &
DeliveryDate< XXX eg infant birth <31dec2014??)
*******************************************************************************
****
*To activate these edits
* 1. Turn off the insheet command above
* Turn on the following commands before the next double line break of "*****
*(depending on whether using C drive or S drive)

*insheet using "S:\QCMRI-RiOAR\FluMum Study National\Data exports\Database
Exports 2014\FluMum 12Dec2014.csv", case
insheet using "C:\MAE for uni\FluMum epi project\Data analysis\Do files\FluMum
12Dec2014.csv", case

*keep StudyID ID Site PlaceScreened Consent Enrolled FluvaxPreg DateSEQ
MaternalDOB LMPDate DeliveryDate ScreenDate ///
*Antenatal MatILI Mat2iLi Mat3iLi Mat4iLi FluvaxPreg Fluvax12mths FluvaxEver
B1Live B1Immune B1Steroids LiveBirth ///
*Mat1Test Mat2Test Mat3Test Mat4Test Mat1FluWeeks Mat2FluWeeks Mat3FluWeeks
Mat4FluWeeks Bmth  ///
*Gestation ScreeningNum B1Wgt SiteCity B1Sex B1HighRisk Heart-ImmuneMedspreg
PregSmoker AustralianBorn English2 ///
*DayCare IndoorSmoke ATSIMum ATSIBaby HouseholdSmoker Education
ReasonWithdrawn vpflupregdate
*******************************************************************************
****
*******************************************************************************
****

save FluMum_nested.dta, replace

*NOTE: all participants must be >17yrs to be eligible to consent to be in this
study
*NOTE: all participants must be able to speak English to be eligible to
consent to be in this study
*NOTE: Fields containing potentially identifiable data and/or no values or
relevance have been deleted
```

```
*STUDY ID
codebook StudyID
*all missing data here for StudyID, now check ID
codebook ID
* confirm ID is a unique number
bysort ID: assert [_N]==1


*STUDY SITE Q12.03
codebook Site
tab Site, miss
sort Site ID
*NOTE:Sites 1-6
label define labelSite  1 "Darwin" 2 "Brisbane" 3 "Sydney" 4 "Melbourne" 5
"Adelaide" 6 "Perth"
numlabel, add
label values Site labelSite
tab Site, miss


*PLACE SCREENED (Screening log)
codebook PlaceScreened
replace PlaceScreened = "1" if PlaceScreened == "Private Hospital"
replace PlaceScreened ="0" if PlaceScreened =="Public Hospital"
replace PlaceScreened="2" if PlaceScreened =="Community Health Centre"
replace PlaceScreened="3" if PlaceScreened =="Postnatal Clinic"
replace PlaceScreened="4" if PlaceScreened =="Antenatal Clinic"
replace PlaceScreened="5" if PlaceScreened =="Other" | PlaceScreened
=="Birthing Centre"
replace PlaceScreened="5" if PlaceScreened =="Oher"
destring PlaceScreened, replace
label define labelPlaceScreened 0 "Public Hospital" 1"Private Hospital" 2
"Community Health Centre" 3 "Postnatal Clinic" ///
4 "Antenatal Clinic" 5 "Other"
label values PlaceScreened labelPlaceScreened
tab PlaceScreened, miss
bysort PlaceScreened: tab FluvaxPreg
*Create a categorical variable for "Place of birth" that differentiates
"Public hospital" from "Private hospital"
gen PlaceBirth=0 if PlaceScreened==0
replace PlaceBirth=1 if PlaceScreened==1
replace PlaceBirth=2 if PlaceScreened>1 & PlaceScreened<.
label var PlaceScreened "Place of birth of infant"
label define labelPlaceBirth 0 "Public hosp" 1 "Private hosp" 2
"Other/unspecified"
label values PlaceBirth labelPlaceBirth
* now cross check recoding makes sense
tab PlaceScreened PlaceBirth, miss


*CONSENT Q1.02
codebook Consent
label var Consent "Informed consent obtained"
replace Consent="0" if Consent =="No"
replace Consent="1" if Consent =="Yes"
destring Consent, replace
label define labelYesNo 0 "(0)No"  1 "(1)Yes" 9 "(9)Unk" 10 "(10)Dcl"
label values Consent labelYesNo
tab Consent, miss
tab Consent Site, miss

codebook ReasonNotEnrolled

*RECODING YES/NO Q's & DESTRINGING
*MATERNAL RESPIRATORY ILLNESS Q's
foreach var of varlist MatILI Mat2iLi Mat3iLi Mat4iLi FluvaxPreg Fluvax12mths
FluvaxEver B1Live B1Immune B1Steroids LiveBirth English1 StaySix Age17
FUWindow{
      codebook `var'
      replace `var'="0" if `var'=="No"
      replace `var'="1" if `var' =="Yes"
      replace `var'=".u" if `var' =="Unknown" | `var'=="Unk"
      replace `var'=".d" if `var'=="Declined" | `var'=="Dcl"
      destring `var', replace
```

```
        label values `var' labelYesNo
        codebook `var'
        tab `var',miss
}
label var MatILI "Maternal resp illness during pregnancy"
label var Mat2iLi "2nd maternal resp illness during pregnancy"
label var Mat3iLi "3rd maternal resp illness during pregnancy"
label var Mat4iLi "4th maternal resp illness during pregnancy"
label var FluvaxPreg "Maternal flu vaccine during pregnancy"
label var Fluvax12mths "Maternal flu vaccine 12 months prior to pregnancy"
label var FluvaxEver "Ever had a flu vaccine?"
label var B1Live "Live birth this pregnancy"
label var B1Immune "Infant diagnosed with immunosuppressive condition"
label var B1Steroids "Infant given steroids since birth (1st 8 weeks)"
label var LiveBirth "Live birth this pregnancy"
label var English1 "English speaking"
label var Age17 "Participant over 17 years of age"
label var StaySix "Eligibility 6 months"
label var FUWindow "Elligibility within follow up window"


*This section on heirarchy for consent/consort code is written by Ross Andrews
*make a hierarchy so Consent minus Withdrawn = Active, then Complete6mth_pc =
0 if Lost to follow-up, 1 if Status=Complete
gen Withdrawn=0 if Consent==1
replace Withdrawn=1 if Status=="Withdrawn"
tab ReasonWithdrawn Withdrawn
replace Withdrawn=0 if (substr(ReasonWithdrawn,1,4)=="Loss" |
substr(ReasonWithdrawn,1,4)=="Lost" | ///
substr(ReasonWithdrawn,1,4)=="lLos") & Withdrawn==1
replace Withdrawn=0 if (substr(ReasonWithdrawn,1,11)=="Other - con") &
Withdrawn==1
label var Withdrawn "Withdrawn (recoded)"
*bysort Consent: tab Withdrawn Status, miss
gen Active=0 if Withdrawn==0
replace Active=1 if Status=="Active" & Active==0
label var Active "Active (recoded 0=Eligible participant no longer active)"
*bysort Consent: tab Active Status, miss


tab ReasonWithdrawn
label define labelReasonWithdrawn 0 "Not Withdrawn" 1 "OutsideStudyWindow" 2
"WithdrewConsent" 3 "MovedOverseas" 4 "LostToFollow-up" ///
5 "DeathBaby" 6 "DeathMother" 7 "Insufficient English" 8 "Other" 9 "Unknown"
88 "DataEntryError"

gen ReasonWithdrawn_calc=0 if Withdrawn==0
replace ReasonWithdrawn_calc=1 if substr(ReasonWithdrawn,1,7)=="Outside"
replace ReasonWithdrawn_calc=2 if (substr(ReasonWithdrawn,11,7)=="Consent" |
substr(ReasonWithdrawn,11,7)=="consent")
replace ReasonWithdrawn_calc=2 if (substr(ReasonWithdrawn,10,7)=="Consent" |
substr(ReasonWithdrawn,10,7)=="consent")
replace ReasonWithdrawn_calc=3 if (substr(ReasonWithdrawn,1,5)=="Moved" |
substr(ReasonWithdrawn,1,5)=="moved")
replace ReasonWithdrawn_calc=4 if (substr(ReasonWithdrawn,1,4)=="Loss" |
substr(ReasonWithdrawn,1,4)=="Lost" | ///
substr(ReasonWithdrawn,1,4)=="lLos")
replace ReasonWithdrawn_calc=5 if (substr(ReasonWithdrawn,1,10)=="Death of B"
| substr(ReasonWithdrawn,1,10)=="Death of b")
replace ReasonWithdrawn_calc=6 if (substr(ReasonWithdrawn,1,10)=="Death of M"
| substr(ReasonWithdrawn,1,10)=="Death of m")
replace ReasonWithdrawn_calc=7 if (substr(ReasonWithdrawn,1,6)=="Insuff")
replace ReasonWithdrawn_calc=8 if (substr(ReasonWithdrawn,1,5)=="Other" |
substr(ReasonWithdrawn,1,5)=="other")
*"Other contact details not current" = lost to follow-up
replace ReasonWithdrawn_calc=4 if (substr(ReasonWithdrawn,1,11)=="Other -
con")


replace ReasonWithdrawn_calc=9 if (substr(ReasonWithdrawn,1,3)=="Unk" |
substr(ReasonWithdrawn,1,3)=="unk")
replace ReasonWithdrawn_calc=88 if (substr(ReasonWithdrawn,1,5)=="Error")
*Note 5 records from Brisbane with no analysable data
replace ReasonWithdrawn_calc=88 if ID=="DC5981CA-9F78-9149-B991-1815B1B06C0B"
```

```
replace ReasonWithdrawn_calc=88 if ID=="7A55F94F-5EA3-8F4E-97B8-12BBB253CE20"
replace ReasonWithdrawn_calc=88 if ID=="E4F97F80-1DD2-CD4F-B682-33DBB6181FFD"
replace ReasonWithdrawn_calc=88 if ID=="B5FC3ED0-9893-B046-B6E8-590A2ADD2D13"
replace ReasonWithdrawn_calc=88 if ID=="833D2434-F69F-45E6-BD14-0148E5986AE1"

replace ReasonWithdrawn_calc=9 if Status=="Withdrawn" & Consent==1 &
Withdrawn==1 & ReasonWithdrawn_calc==.

*Some records coded as LostToFollow-up but had not consented and had not
completed eligibility criteria
bysort Site: l ScreeningNum MaternalDOB DeliveryDate ScreenDate DateSEQ ///
Consent English1 FUWindow StaySix Age17 Health FluvaxPreg Withdrawn
ReasonWithdrawn_calc if ///
ReasonWithdrawn_calc==4 & Consent~=1 & English1~=1 & FUWindow~=1 & StaySix~=1
& Age17~=1, noobs

replace ReasonWithdrawn_calc=. if ReasonWithdrawn_calc==4 & Consent~=1 &
English1~=1 & FUWindow~=1 & StaySix~=1 & Age17~=1
replace Withdrawn=. if Withdrawn==0 & ReasonWithdrawn_calc==. & Consent~=1 &
English1~=1 & FUWindow~=1 & StaySix~=1 & Age17~=1

*Some records coded as WithdrewConsent but appear to have completed Part A.
Assume LTFU unless advised otherwise by Site
tab ReasonWithdrawn_calc FluvaxPreg if ReasonWithdrawn_calc==2, miss

label values ReasonWithdrawn_calc labelReasonWithdrawn
label var ReasonWithdrawn_calc "Reason Withdrawn or LTFU (calculated)"

sort Site DateSEQ
bysort Site ReasonWithdrawn_calc: l ScreeningNum ScreenDate MaternalLastName
MaternalDOB DeliveryDate ///
DateSEQ Consent English1 FUWindow StaySix Age17 Health FluvaxPreg ///
Withdrawn  if (ReasonWithdrawn_calc==2 | ReasonWithdrawn_calc==8 |
ReasonWithdrawn_calc==9) ///
 & (FluvaxPreg==0 | FluvaxPreg==1), noobs

gen chkReasonWithdrawn=1 if (ReasonWithdrawn_calc==2 | ReasonWithdrawn_calc==8
| ReasonWithdrawn_calc==9) ///
 & (FluvaxPreg==0 | FluvaxPreg==1)
label var chkReasonWithdrawn "Check if reason withdrawn should be Lost to
Follow-up"
replace Withdrawn=0 if chkReasonWithdrawn==1 & Withdrawn==1
replace ReasonWithdrawn_calc=4 if chkReasonWithdrawn==1 & ///
(ReasonWithdrawn_calc==2 | ReasonWithdrawn_calc==8 | ReasonWithdrawn_calc==9)
* Coding written by Ross Andrews complete

**DATES
*DATESEQ Q1.04, MATERNAL DATE OF BIRTH Q2.03, LMP Date Q12.08
codebook MaternalDOB
*1. Create a variable to calculate the maternal age at delivery
*Format string date variables (note DeliveryDate & ScreenDate were numeric,
others were strings)
*Note-dates are MDY in excel dataset,need to change these so they look like
DMY
foreach var of varlist DateSEQ MaternalDOB LMPDate DeliveryDate Date1Given
ScreenDate{
      codebook `var'
      replace `var'="" if `var'=="?"
      replace `var'="10Oct1010" if `var'=="9/09/0909" | `var'=="10/10/1010"
      gen `var'f=date(`var', "DMY")
      format `var'f %td
      drop `var'
      rename *f *
      replace `var'=.u if `var'==d(10Oct1010)
      codebook `var'
}
drop if Withdrawn==1
tab Site FluvaxPreg if Consent==1

*ENROLLED
codebook Enrolled
```

```
tab Enrolled Site, miss
tab Enrolled Site if Consent==1
bysort Enrolled: tab Site FluvaxPreg, col

foreach var of varlist MatILI Mat2iLi Mat3iLi Mat4iLi Fluvax12mths FluvaxEver{
tab `var' FluvaxPreg, col
}
gen MatAge=(DeliveryDate-MaternalDOB)/365.25 if MaternalDOB>d(10oct1010)&
MaternalDOB<.
*Then create histogram to determine whether data are normally distributed for
maternal age at delivery.
hist MatAge
*Data are normally distributed
codebook MatAge
*sort MatAge by FluvaxPreg
tabstat MatAge, by (Site) stat (n mean min p25 p50 p75 max)
tabstat MatAge, by (FluvaxPreg) stat (n mean min p25 p50 p75 max)

*ANTENATAL (WEEKS PREGNANT AT FIRST ANTENATAL VISIT) Q4.02
codebook Antenatal
tab Antenatal, miss
label var Antenatal "Wks @ 1st antenatal care"
* Q4.02 says enter 0 if not attended any antenatal care
*Create a categorical variable for antenatal care that differentiates "no
care" from "early care" & "late care"
gen AntenatalBy16=0 if Antenatal==0
replace AntenatalBy16=1 if Antenatal<17
replace AntenatalBy16=2 if Antenatal>16 & Antenatal<99
replace AntenatalBy16=.u if Antenatal==99
replace AntenatalBy16=.m if Antenatal==100
label var AntenatalBy16 "Self-reported antenatal care by 16wks (<17wks)"
label define labelAntenatalBy16 0 "No antenatal care" 1 "1st antenatal care by
16wks" 2 "1st antenatal care after 16wks" ///
.u "unk wks preg@1st antenatal care" .d "declined wks preg@1st antenatal care"
label values AntenatalBy16 labelAntenatalBy16
* now cross check recoding makes sense
tab Antenatal AntenatalBy16, miss
gen MeanGest=Antenatal if Antenatal>0 & Antenatal<99
*tabstat MeanGest, by (FluvaxPreg) stat (n mean min p25 p50 p75 max)is
performed at the end

* MATERNAL INFLUENZA LIKE ILLNESS (ILI) IN PREGNANCY
tab MatILI
*some mum's have had more than one ILI in pregnancy-how to account for this?
tab FluvaxPreg if MatILI==1
tab MatILI if FluvaxPreg==1

*TESTS DONE FOR RESP ILLNESS Q5.01, Q5.07, Q6.02, Q6.08
*Current data export on tests not easily analysable

foreach var of varlist Mat1Test Mat2Test Mat3Test Mat4Test{
        codebook `var'
        tab `var',miss
}
*generate categorical variable for maternal tests for 1st resp illness
gen RespTest1=0 if Mat1Test==0
replace RespTest1=1 if Mat1Test==1 | Mat1Test==2 | Mat1Test==3
replace RespTest1=2 if Mat1Test>10 & Mat1Test<.
replace RespTest1=.u if Mat1Test==9
replace RespTest1=.d if Mat1Test==10
label var RespTest1 "Type of 1st TEST for resp illness in pregnancy"
label define labelRespTest1 0 "No test" 1 "Blood test, nose OR throat swab" 2
"More than 1 test" .u "Unknown" ///
.d "Missing data"
label values RespTest1 labelRespTest1
* now cross check recoding makes sense
tab RespTest1, miss
tab RespTest1 if MatILI==1

*generate categorical variable for maternal tests for 2nd resp illness
gen RespTest2=0 if Mat2Test==0
```

```
replace RespTest2=1 if Mat2Test==1 | Mat2Test==2 | Mat2Test==3
replace RespTest2=2 if Mat2Test>10 & Mat2Test<.
replace RespTest2=.u if Mat2Test==9
replace RespTest2=.d if Mat2Test==10
label var RespTest2 "Type of 2nd TEST for resp illness in pregnancy"
label define labelRespTest2 0 "No test" 1 "Blood test, nose OR throat swab" 2
"More than 1 test" .u "Unknown" ///
.d "Missing data"
label values RespTest2 labelRespTest2
* now cross check recoding makes sense
tab RespTest2, miss
tab RespTest2 if MatILI==1


*generate categorical variable for maternal tests for 3rd resp illness
gen RespTest3=0 if Mat3Test==0
replace RespTest3=1 if Mat3Test==1 | Mat3Test==2 | Mat3Test==3
replace RespTest3=2 if Mat3Test>10 & Mat3Test<.
replace RespTest3=.u if Mat3Test==9
replace RespTest3=.d if Mat3Test==10
label var RespTest3 "Type of 3rd TEST for resp illness in pregnancy"
label define labelRespTest3 0 "No test" 1 "Blood test, nose OR throat swab" 2
"More than 1 test" .u "Unknown" ///
.d "Missing data"
label values RespTest3 labelRespTest3
* now cross check recoding makes sense
tab RespTest3, miss
tab RespTest3 if MatILI==1


*generate categorical variable for maternal tests for 4th resp illness
gen RespTest4=0 if Mat2Test==0
replace RespTest4=1 if Mat4Test==1 | Mat4Test==2 | Mat4Test==3
replace RespTest4=2 if Mat4Test>10 & Mat4Test<.
replace RespTest4=.u if Mat4Test==9
replace RespTest4=.d if Mat4Test==10
label var RespTest4 "Type of 4th TEST for resp illness in pregnancy"
label define labelRespTest4 0 "No test" 1 "Blood test, nose OR throat swab" 2
"More than 1 test" .u "Unknown" ///
.d "Missing data"
label values RespTest4 labelRespTest4
* now cross check recoding makes sense
tab RespTest4, miss
tab RespTest4 if MatILI==1


*I want to create categorical variables to separate out the trimesters and
display the results in a table by trimester.
*WEEKS PREGNANT IF VISITED THE DOCTOR FOR AN ILI & HAD A TEST Q5.04, Q5.10,
Q6.05, Q6.11
*generate new variable to create categories for trimesters
foreach var of varlist Mat1FluWeeks-Mat4FluWeeks{
        codebook `var'
}
*generate categorical variable for trimester at 1st visit to Dr for flu
gen GestTest=0 if Mat1FluWeeks==0
replace GestTest=1 if Mat1FluWeeks<=13
replace GestTest=2 if Mat1FluWeeks>=14 & Mat1FluWeeks<=28
replace GestTest=3 if Mat1FluWeeks>=29 & Mat1FluWeeks<=43
replace GestTest=.u if Mat1FluWeeks==99
replace GestTest=.d if Mat1FluWeeks==100
label var GestTest "Trimester in which 1st test for flu occurred"
label define labelGestTest 1 "1st trimester test for flu" 2 "2nd trimester
test for flu" 3 "3rd trimester test for flu" ///
.u "unknown trimester when visited for flu" .d "declined"
label values GestTest labelGestTest
* now cross check recoding makes sense
codebook GestTest
*cross tab against MatFluWeeks to see if new variable matches as intended (it
does!)
tab Mat1FluWeeks GestTest, miss
tab GestTest FluvaxPreg, col
tab Mat1FluWeeks if Mat1FluWeeks <99 & Mat1FluWeeks >0
replace Mat1FluWeeks=.m if Mat1FluWeeks==0
```

```
replace Mat1FluWeeks=.u if Mat1FluWeeks==99
replace Mat1FluWeeks=.d if Mat1FluWeeks==100
tab Mat1FluWeeks

*generate categorical variable for trimester at 2nd visit for flu
gen GestTest2=0 if Mat2FluWeeks==0
replace GestTest2=1 if Mat2FluWeeks<=13
replace GestTest2=2 if Mat2FluWeeks>=14 & Mat2FluWeeks<=28
replace GestTest2=3 if Mat2FluWeeks>=29 & Mat2FluWeeks<=43
replace GestTest2=.u if Mat2FluWeeks==99
replace GestTest2=.m if Mat2FluWeeks==100
label var GestTest2 "Trimester in which 2nd test for flu occurred"
label define labelGestTest2 1 "1st trimester test for flu" 2 "2nd trimester
test for flu" 3 "3rd trimester test for flu" ///
.u "unknown trimester when tested for flu" .m "missing data"
label values GestTest2 labelGestTest2
* now cross check recoding makes sense
tab Mat2FluWeeks GestTest2, miss
tab GestTest2 FluvaxPreg, col

*generate categorical variable for trimester at 3rd visit for flu
gen GestTest3=0 if Mat3FluWeeks==0
replace GestTest3=1 if Mat3FluWeeks<=13
replace GestTest3=2 if Mat3FluWeeks>=14 & Mat3FluWeeks<=28
replace GestTest3=3 if Mat3FluWeeks>=29 & Mat3FluWeeks<=43
replace GestTest3=.u if Mat3FluWeeks==99
replace GestTest3=.m if Mat3FluWeeks==100
label var GestTest3 "Trimester in which 3rd test for flu occurred"
label define labelGestTest3 1 "1st trimester test for flu" 2 "2nd trimester
test for flu" 3 "3rd trimester test for flu" ///
.u "unknown trimester when tested for flu" .m "missing data"
label values GestTest3 labelGestTest3
* now cross check recoding makes sense
tab Mat3FluWeeks GestTest3, miss
tab GestTest3 FluvaxPreg, col

*generate categorical variable for trimester at 4th visit for flu
gen GestTest4=0 if Mat4FluWeeks==0
replace GestTest4=1 if Mat4FluWeeks<=13
replace GestTest4=2 if Mat4FluWeeks>=14 & Mat4FluWeeks<=28
replace GestTest4=3 if Mat4FluWeeks>=29 & Mat4FluWeeks<=43
replace GestTest4=.u if Mat4FluWeeks==99
replace GestTest4=.m if Mat4FluWeeks==100
label var GestTest4 "Trimester in which 4th test for flu occurred"
label define labelGestTest4 1 "1st trimester test for flu" 2 "2nd trimester
test for flu" 3 "3rd trimester test for flu" ///
.u "unknown trimester when tested for flu" .m "missing data"
label values GestTest4 labelGestTest4
* now cross check recoding makes sense
tab Mat4FluWeeks GestTest4, miss
tab GestTest4 FluvaxPreg, col

*DATE OF DELIVERY Q12.01 (dd/mmm/yyyy)
*create year and month of delivery
gen Birthyear = year(DeliveryDate)
label var Birthyear "Year infant born"
gen Birthmonth = month(DeliveryDate)
label var Birthmonth "Month infant born"
label define labelmonth 1 "Jan" 2 "Feb" 3 "Mar" 4 "Apr" 5 "May" 6 "Jun" 7
"Jul" 8 "Aug" 9 "Sep" 10 "Oct" 11 "Nov" 12 "Dec"
label values Birthmonth labelmonth
gen Birthyrmth = Birthyear + (Birthmonth*0.01)
label var Birthyrmth "Year month infant born"
tab Birthyrmth, miss

*BIRTHMONTH Q12.04
codebook Bmth
tab Bmth, miss
tab Bmth Site, col

*LIVEBIRTHS Q12.05
```

```
codebook LiveBirth
tab LiveBirth, miss
tab LiveBirth
label var LiveBirth "Live Birth"
label values LiveBirth labelYesNo
tab Site LiveBirth, miss
tab LiveBirth


*GESTATION IN WEEKS AT DELIVERY (Q12.07)
*Definition/reference came from AIHW website accessed 18Dec2014 babies are
preterm if born before 37 completed wks
codebook Gestation
tab Gestation, miss
br if Gestation<25 | (Gestation>42 & Gestation<.)
list ScreeningNum StudyID Site Gestation if Gestation<25 | (Gestation>42 &
Gestation<.), noobs
bysort Site: list ScreeningNum StudyID Site Enrolled Consent DeliveryDate
Gestation if Gestation<25 | (Gestation>42 & Gestation<.), noobs
tab Gestation if Gestation <38 & Gestation >10
gen Gest37comp=1 if Gestation>20 & Gestation<38
replace Gest37comp=0 if Gestation>=38 & Gestation<.
label var Gest37comp "Gestation <37 completed weeks"
tab Gest37comp FluvaxPreg, col
cs Gest37comp FluvaxPreg
tabstat Gestation, by (FluvaxPreg) stat (n mean min p25 p50 p75 max)
tabstat Gestation, by (Site) stat (n mean min p25 p50 p75 max)


*PREMATURITY
*generate categorical variable for gestation =<38 weeks & >=38 weeks (that is
less than 37 completed weeks & > 37 completed weeks)
gen GestWeeks=0 if Gestation==0
replace GestWeeks=1 if Gestation>24 & Gestation<=29
replace GestWeeks=2 if Gestation>29 & Gestation<=34
replace GestWeeks=3 if Gestation>34 & Gestation<=37
replace GestWeeks=4 if Gestation>37 & Gestation<43
replace GestWeeks=.u if Gestation==99
replace GestWeeks=.d if Gestation==100
label var GestWeeks "Gestation at delivery-preterm birth"
label define labelGestWeeks 1 "<=29wks gest. @ delivery" 2 "30-34 wks gest @
delivery " 3 "35-37 wks gest @ delivery " 4 ">38 wks gest @ delivery" ///
.u "unk wks preg@delivery" .d "declined response"
label values GestWeeks labelGestWeeks
*Now check to see recoding makes sense
tab Gestation GestWeeks, miss
*It does!
tab GestWeeks Site, col
tab GestWeeks FluvaxPreg, col chi
*Generate new variable for severe prem babies born under 30 weeks
gen Prem30=1 if GestWeeks==1
replace Prem30=0 if GestWeeks==4
label var Prem30 "<=29wks gest. @ delivery"
label define labelPrem30 0 ">38 wks gest @ delivery" 1 "<=29wks gest. @
delivery"
label values Prem30 labelPrem30
tab GestWeeks Prem30 , miss
cs Prem30 FluvaxPreg
**Generate new variable for prem babies born under 35 weeks
gen Prem35=1 if GestWeeks==1 | GestWeeks==2
replace Prem35=0 if GestWeeks==4
label var Prem35 "<35wks gest. @ delivery"
label define labelPrem35 0 ">38 wks gest @ delivery" 1 "<35wks gest. @
delivery"
label values Prem35 labelPrem35
tab GestWeeks Prem35 , miss
cs Prem35 FluvaxPreg


*BIRTHWEIGHT (in grams) Q14.03
*References for low birthweight are from AIHW website accessed 18Dec2014
codebook B1Wgt
hist B1Wgt
mean B1Wgt
```

```
tabstat B1Wgt, by (Site) stat (n mean min p25 p50 p75 max)
tabstat B1Wgt, by (FluvaxPreg) stat (n mean min p25 p50 p75 max)
summ B1Wgt, detail
*Need to make categorical variable for <2500g =2500-3999g >=4000g
gen Lbwt=0 if B1Wgt==0
replace Lbwt=1 if B1Wgt<2500
replace Lbwt=2 if B1Wgt>=2500 & B1Wgt<=3999
replace Lbwt=3 if B1Wgt>=4000 & B1Wgt<=6000
*Birthweight needs to be a minimum of 400g
tab B1Wgt Lbwt if B1Wgt<401, miss
replace Lbwt=.u if B1Wgt<401
replace Lbwt=.d if B1Wgt==100
tab B1Wgt Lbwt if B1Wgt<401, miss
label var Lbwt "Low birth weight at delivery"
label define labelLbwt 1 "<2500g bweight " 2 ">=2500g-<=3999g bweight " 3
">=4000g bweight " ///
.u "unk birthweight" .d "declined response"
label values Lbwt labelLbwt
* now cross check recoding makes sense
*It does yay!
tab Lbwt Site, miss
tab Lbwt FluvaxPreg, miss
tab Lbwt FluvaxPreg, col chi*LOW BIRTHWEIGHT-Infants less than 2500g
gen LowBwt=1 if B1Wgt<2500
replace LowBwt=0 if B1Wgt>=2500 & B1Wgt<6000
replace Lbwt=.u if B1Wgt<401
replace Lbwt=.d if B1Wgt==100
label var LowBwt "Infant less than 2500g"
label define labelLowBwt 0 ">2500g bweight" 1 "<2500g bweight" .u "unk
birthweight" .d "declined response"
label values LowBwt labelLowBwt
tab LowBwt FluvaxPreg, col chi
cs LowBwt FluvaxPreg
*VERY LOW BIRTHWEIGHT-Infants less than 1500g
gen VLowBwt=1 if B1Wgt<1500
replace VLowBwt=0 if B1Wgt>=1500 & B1Wgt<6000
replace VLowBwt=.u if B1Wgt<401
replace VLowBwt=.d if B1Wgt==100
label var VLowBwt "Infant less than 1500g"
label define labelVLowBwt 0 ">1500g bweight" 1 "<1500g bweight" .u "unk
birthweight" .d "declined response"
label values VLowBwt labelVLowBwt
tab VLowBwt FluvaxPreg, col chi
cs VLowBwt FluvaxPreg
*EXTREMELY LOW BIRTHWEIGHT-Infants less than 1000g
gen ELowBwt=1 if B1Wgt<1000
replace ELowBwt=0 if B1Wgt>=1000 & B1Wgt<6000
replace ELowBwt=.u if B1Wgt<401
replace ELowBwt=.d if B1Wgt==100
label var ELowBwt "Infant less than 1000g"
label define labelELowBwt 0 " >1000g bweight" 1 "<1000g bweight" .u "unk
birthweight" .d "declined response"
label values ELowBwt labelELowBwt
tab ELowBwt FluvaxPreg, col chi
cs ELowBwt FluvaxPreg
cs ELowBwt FluvaxPreg, exact

*LARGE FOR GESTATIONAL AGE->4000G
gen LGA=0 if B1Wgt<4000
replace LGA=1 if B1Wgt>=4000 & B1Wgt<=6000
replace LGA=.u if B1Wgt<401
replace LGA=.d if B1Wgt==100
label var LGA "LGA"
label define labelLGA 0 "<4000g bweight " 1 ">=4000g bweight " .u "unk
birthweight" .d "declined response"
label values LGA labelLGA
tab LGA FluvaxPreg, col chi
cs LGA FluvaxPreg
*NORMAL FOR GESTATIONAL AGE-2500-3999g
gen NGA=1 if B1Wgt>=2500 & B1Wgt<=4000
replace NGA=0 if B1Wgt>=4000 | B1Wgt<=2500
```

```
replace NGA=.u if B1Wgt<401
replace NGA=.d if B1Wgt==100
label var NGA "NGA"
label define labelNGA 0 ">=4000g bweight & <2500g " 1 "Normal birthweight " .u
"unk birthweight" .d "declined response"
label values NGA labelNGA
tab NGA FluvaxPreg, col chi
cs NGA FluvaxPreg


*GENDER (infant) Q14.04
codebook B1Sex
label var B1Sex "Gender of infant"
replace B1Sex="0" if B1Sex=="I"
replace B1Sex="1" if B1Sex=="M"
replace B1Sex="2" if B1Sex=="F"
replace B1Sex="10" if B1Sex=="Dcl" | B1Sex=="Declined"
destring B1Sex, replace
label define labelB1Sex 0 "Indeterminate" 1 "Male" 2 "Female" 10 "Declined"
label values B1Sex labelB1Sex
tabstat B1Sex, by (Site) stat (n mean min p25 p50 p75 max)
tab B1Sex FluvaxPreg, col

gen InfantSex=0 if B1Sex==0
replace InfantSex=0 if B1Sex==1
replace InfantSex=1 if B1Sex>1 & B1Sex<.
label var InfantSex "Sex of infant"
label define labelInfantSex 0 "Male" 1 "Female" 2 "Other/unspecified"
label values InfantSex labelInfantSex
* now cross check recoding makes sense
tab InfantSex FluvaxPreg, col chi
cs InfantSex FluvaxPreg

*IF YES, NAME OF IMMUNE DISORDER Q14.09
*Lots of different text responses for this variable, not sure whether will
need to include or not
codebook B1ImmuneName
*tab B1ImmuneName, miss
*tab B1ImmuneName

*IF YES, REASON GIVEN STEROIDS Q14.11
*as above
codebook B1Steroid_reason

*BABY ILLNESS REQUIRIING MEDICAL FOLLOW-UP OR HOSP Q14.12
codebook B1HighRisk

*IF YES, NAME OF MEDICAL CONDITION Q 14.13
*as above
codebook B1HighRiskName
*tab B1HighRiskName

**MATERNAL RISK FACTORS Q'S 17.01-17.11, Q17.13, Q18.03,18.06
*MOTHER EVER BEEN TOLD SHE HAS THE FOLLOWING CONDITIONS
foreach var of varlist Heart-ImmuneMedspreg PregSmoker AustralianBorn English2
DayCare IndoorSmoke{
      codebook `var'
      replace `var'="0" if `var'=="No"
      replace `var'="1" if `var' =="Yes"
      replace `var'="9" if `var' =="Unknown" | `var'=="Unk"
      replace `var'="10" if `var'=="Declined" | `var'=="Dcl"
      destring `var', replace
      label values `var' labelYesNo
      codebook `var'
      tab `var' FluvaxPreg,miss
      tab `var' FluvaxPreg, col
}
label var Heart "Heart disease"
label var Hypertension "Hypertension"
label var Pneumonia "Severe pneumonia requiring hospitalisation during
pregnancy"
label var Bronchitis "Chronic resp condition"
```

```
label var Immune "Immunosuppressive condition"
label var Cancer "Cancer"
label var Diabetespreg "Diabetes in pregnancy"
label var ImmuneMedspreg "Immunosuppressive meds in pregnancy"
label var PregSmoker "Cigarette smoking in pregnancy"
label var AustralianBorn "Australian born"
label var English2 "Is English main language spoken at home?"
label var DayCare "Any children who attend day care?"
label var IndoorSmoke "Regularly exposed to indoor tobacco smoke during
pregnancy"

*RISK FACTORS (any condition listed in the Aust Immun Handbook, same as Q's 17
in workbook)
gen RiskFact=.
label var RiskFact "Maternal Risk Factors (Co-morbidities)"
foreach var of varlist Heart-ImmuneMedspreg {
tab `var' RiskFact, miss
replace RiskFact=0 if `var'<9 & RiskFact~=1
replace RiskFact=1 if `var'==1
tab `var' RiskFact, miss
}
label values RiskFact labelYesNo
tab RiskFact FluvaxPreg, col chi
cs RiskFact FluvaxPreg

*MATERNAL SELF-REPORTED SMOKING IN PREG Q17.13
codebook PregSmoker
tab PregSmoker FluvaxPreg, col
*MATERNAL SELF-REPORTED EXPOSURE TO INDOOR TOBACCO SMOKE IN PREG Q18.16
codebook IndoorSmoke
tab IndoorSmoke FluvaxPreg, miss
tab IndoorSmoke FluvaxPreg, col
cs IndoorSmoke FluvaxPreg

*MOTHER IDENTIFIES AS ABORIGINAL AND/OR TORRES STRAIT ISLANDER Q.18.01
*String variables need to change to numerical, then binary
foreach var of varlist ATSIMum{
        codebook `var'
        replace `var'="0" if `var'=="No"
        replace `var'="1" if `var' =="AB"
        replace `var'="2" if `var' =="TSI"
        replace `var'="3" if `var' =="Both"
        replace `var'="9" if `var' =="Unknown" | `var'=="Unk"
        replace `var'="10" if `var'=="Declined" | `var'=="Dcl"
        destring `var', replace
        label define labelATSIMum 0 "No" 1 "Yes" 2 "TSI" 3 "Both" 9 "Unk" 10
"Dcl"
        label values `var' labelATSIMum
        codebook `var'
        tab `var',miss
}
*BABY IDENTIFIES AS ABORIGINAL AND/OR TORRES STRAIT ISLANDER Q.18.02
foreach var of varlist ATSIBaby{
        codebook `var'
        replace `var'="0" if `var'=="No"
        replace `var'="1" if `var' =="AB"
        replace `var'="2" if `var' =="TSI"
        replace `var'="3" if `var' =="Both"
        replace `var'="9" if `var' =="Unknown" | `var'=="Unk"
        replace `var'="10" if `var'=="Declined" | `var'=="Dcl"
        destring `var', replace
        label define labelATSIBaby 0 "No" 1 "Yes" 2 "TSI" 3 "Both" 9 "Unk" 10
"Dcl"
        label values `var' labelATSIBaby
        codebook `var'
        tab `var',miss
}
*The following coding changes ATSIMum and ATSIBaby from categories into a
binary yes/no outcome
*ATSI Mum
gen IndigMum=0 if ATSIMum==0
```

```
replace IndigMum=1 if ATSIMum>0 & ATSIMum<4
label var IndigMum "Aboriginal and/or Torres Strait Islander"
tab IndigMum
tab IndigMum ATSIMum, miss
tab IndigMum Birthyear
tab IndigMum FluvaxPreg, col
*ATSI Baby
gen IndigBaby=0 if ATSIBaby==0
replace IndigBaby=1 if ATSIBaby>0 & ATSIBaby<4
label var IndigBaby "Aboriginal and/or Torres Strait Islander"
tab IndigBaby
tab IndigBaby ATSIBaby, miss
tab IndigBaby FluvaxPreg, col
cs IndigBaby FluvaxPreg

*NUMBER OF HOUSEHOLD SMOKERS Q18.15
codebook HouseholdSmoker
gen HouseExp=0 if HouseholdSmoker==0
replace HouseExp=1 if HouseholdSmoker>=1 & HouseholdSmoker<99
replace HouseExp=.u if HouseholdSmoker==99
replace HouseExp=.d if HouseholdSmoker==100
label var HouseExp "Exposure to household smoke"
label define labelHouseExp 0 "Is not exposed to household smoke" 1 "Exposed to
household smoke" ///
.u "unknown" .d "declined response"
label values HouseExp labelHouseExp
* now cross check recoding makes sense
tab HouseholdSmoker HouseExp, miss
tab HouseExp FluvaxPreg, col chi

*EDUCATION QUALIFICATIONS OF MOTHER Q19.01
codebook Education
label define labelEducation 1 "Did not finish high school" 2 "High school" 3
"Certificate" 4 "Diploma" 5 "Degree" ///
6 "Post grad degree" 10 "Declined"
label values Education labelEducation
tab Education FluvaxPreg if Consent==1, col
*Create a categorical variable for Education that differentiates "Diploma &
under " from "Degree or higher"
gen EducationCat=0 if Education==0
replace EducationCat=0 if Education>0 & Education<=4
replace EducationCat=1 if Education>=5 & Education<7
replace EducationCat=.m if Education==10
label var EducationCat "Education Level of mother"
label define labelEducationCat 0 "Diploma & Under" 1 "Degree or higher" .d
"declined"
label values EducationCat labelEducationCat
* now cross check recoding makes sense
tab EducationCat Education, miss
tab EducationCat FluvaxPreg, col chi
cs EducationCat FluvaxPreg

tab Site FluvaxPreg if Consent==1
bysort Enrolled: tab Site FluvaxPreg, row

*Mean Gestation at 1st Antenatal care presentation
tabstat MeanGest, stat (n mean min p25 p50 p75 max)
tabstat MeanGest, by (FluvaxPreg) stat (n mean min p25 p50 p75 max)
*Following variables used for comparison with FluvaxPreg
foreach var of varlist MatILI IndigMum IndigBaby PregSmoker English2{
      codebook `var'
      tab `var' FluvaxPreg if Consent==1, col miss
      tab `var' FluvaxPreg,miss
}
***UNIVARIATE ANALYSIS
*t-tests for continuous variables with normally distributed data.
ttest Gestation, by (FluvaxPreg)
ttest B1Wgt, by (FluvaxPreg)
ttest MatAge, by (FluvaxPreg)
ttest Antenatal, by (FluvaxPreg)
ttest Mat1FluWeeks, by (FluvaxPreg)
```

```
ttest Gestation, by (MatILI)
ttest B1Wgt, by (MatILI)
ttest MatAge, by (MatILI)


**Chi-square analysis and 95% CI for binary variables
foreach var of varlist PlaceScreened PlaceBirth MatILI SiteCity B1Sex Heart-
ImmuneMedspreg PregSmoker AustralianBorn English2 AntenatalBy16 DayCare-
Education Birthyear Gest37-HouseExp{
      tab `var' FluvaxPreg, col chi
}
*For 95% CI for the remainder of the binary variables (within cohort
*comparisons if required)
bysort FluvaxPreg: ci PlaceBirth
bysort FluvaxPreg: ci MatILI
bysort FluvaxPreg: ci B1Sex
bysort FluvaxPreg: ci Heart-ImmuneMedspreg
bysort FluvaxPreg: ci PregSmoker
bysort FluvaxPreg: ci AustralianBorn
bysort FluvaxPreg: ci AntenatalBy16
bysort FluvaxPreg: ci DayCare-EducationCat
bysort FluvaxPreg: ci Gest37-HouseExp

cs Heart FluvaxPreg
cs Hypertension FluvaxPreg
cs ImmuneMedspreg FluvaxPreg
cs Cancer FluvaxPreg
cs Pneumonia FluvaxPreg
cs Bronchitis FluvaxPreg
cs Immune FluvaxPreg
cs English2 FluvaxPreg
cs DayCare FluvaxPreg

**Crude and relative risks with 95% confidence intervals & p-values.
foreach var of varlist IndigMum Diabetespreg RiskFact PregSmoker MatILI Gest37
Education{
      cs `var' FluvaxPreg
}
*What proportion of women had a flu vaccine in their 1st trimester?
gen FluvaxPregweeks=(DeliveryDate-Date1Given)/7 if DeliveryDate~=. &
Date1Given~=.
*Check for logic
sort FluvaxPregweeks
br FluvaxPregweeks Date1Given DeliveryDate if DeliveryDate~=. & Date1Given~=.


gen GestWeeksFluvax =Gestation-FluvaxPregweeks if Gestation~=. &
FluvaxPregweeks~=.
*generate categorical variable showing trimester when flu vaccine was given in
pregnancy
gen GestTrimFluvax=1 if GestWeeksFluvax >0 & GestWeeksFluvax <14
replace GestTrimFluvax=2 if GestWeeksFluvax>=14 & GestWeeksFluvax<29
replace GestTrimFluvax=3 if GestWeeksFluvax>=29 & GestWeeksFluvax<=43
replace GestTrimFluvax=.u if GestWeeksFluvax==. & FluvaxPreg==1
label var GestTrimFluvax "Trimester in which flu vaccine given"
label define labelGestTrimFluvax 1 "1st trimester fluvax" 2 "2nd trimester
fluvax" 3 "3rd trimester fluvax" ///
.u "unknown trimester" .d "declined"
label values GestTrimFluvax labelGestTrimFluvax

*Look at primary birth outcomes (gestation & birthweights)between those mums
who ///
*had a flu vax in 1st trimester compared to those mums who didn't have a flu
vaccine in pregnancy
ttest Gestation if GestTrimFluvax==1 | FluvaxPreg==0, by (FluvaxPreg)
ttest B1Wgt if GestTrimFluvax==1 | FluvaxPreg==0 , by (FluvaxPreg)

*The proprtion of women who had a flu vaccine in the 1st trimester is...
tab GestTrimFluvax FluvaxPreg, col

*Are infants born in Jan-March more likely to have a mother who was vaccinated
in their ///
```

```
*1st trimester compared to infants born in Apr-Dec?
tab Birthmonth Consent, miss
gen Birthmonthvax=0 if Consent==1 & Birthmonth<=12
replace Birthmonthvax=1 if Birthmonth<4
tab Birthmonthvax Consent, miss
label var Birthmonthvax " Infants born 1=Jan-March, 0= Apr-Dec"
tab GestTrimFluvax Birthmonthvax
bysort Birthmonthvax: tab GestTrimFluvax FluvaxPreg, col miss

*Need to make Gestation & B1Wgt catagorical variables before being able to
calculate relative risks
*foreach var of varlist Gestation B1Wgt{
*       cs `var' FluvaxPreg if GestTrimFluvax==1 | FluvaxPreg==0
*}

* I want to know the birth outcomes of the mum's who
*a) self-reported having a flu vaccine during pregnancy vs those who didn't
(done)
*b) had an ILI (done) see t-test results above
*c) had an ILI & had a test to describe trimester & flu season
*d) had an ILI and DID NOT have a test

* did NOT have an ILI (MatILI==0)

log close
```

Appendix 2.3.   Communicable Disease Control (CDC) conference presentation, Brisbane, June 2015

Appendix 2.3.   Communicable Disease Control (CDC)

FluMum sites 2012-2014

Research question

Differences in birthweights (grams)	Differences in gestation (weeks)
Flu vaccine in pregnancy?	Flu vaccine in pregnancy?
Yes No	Yes No
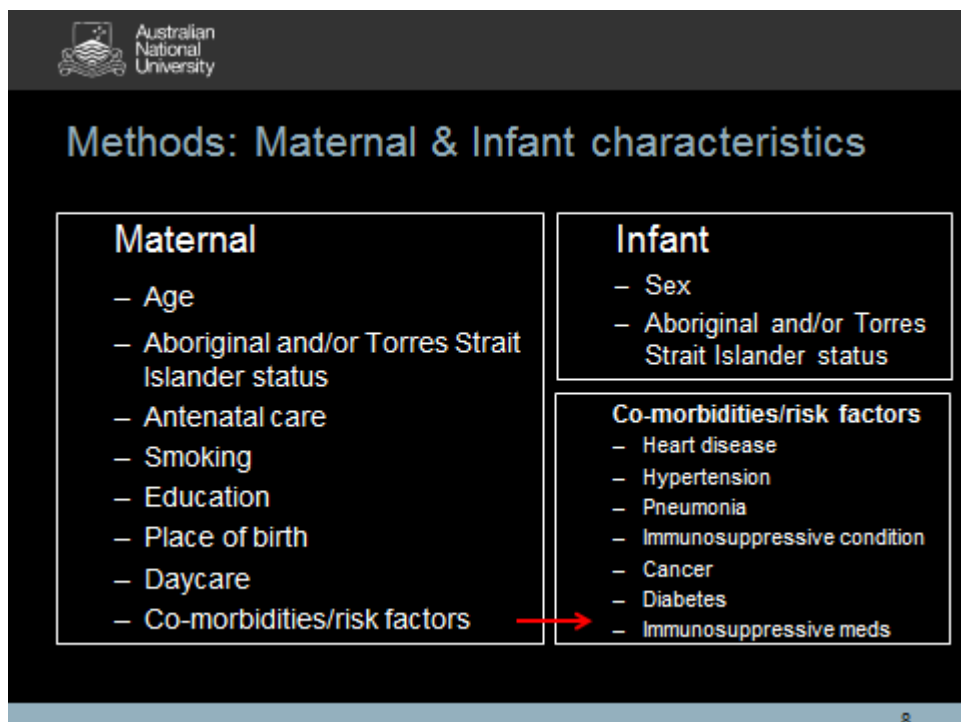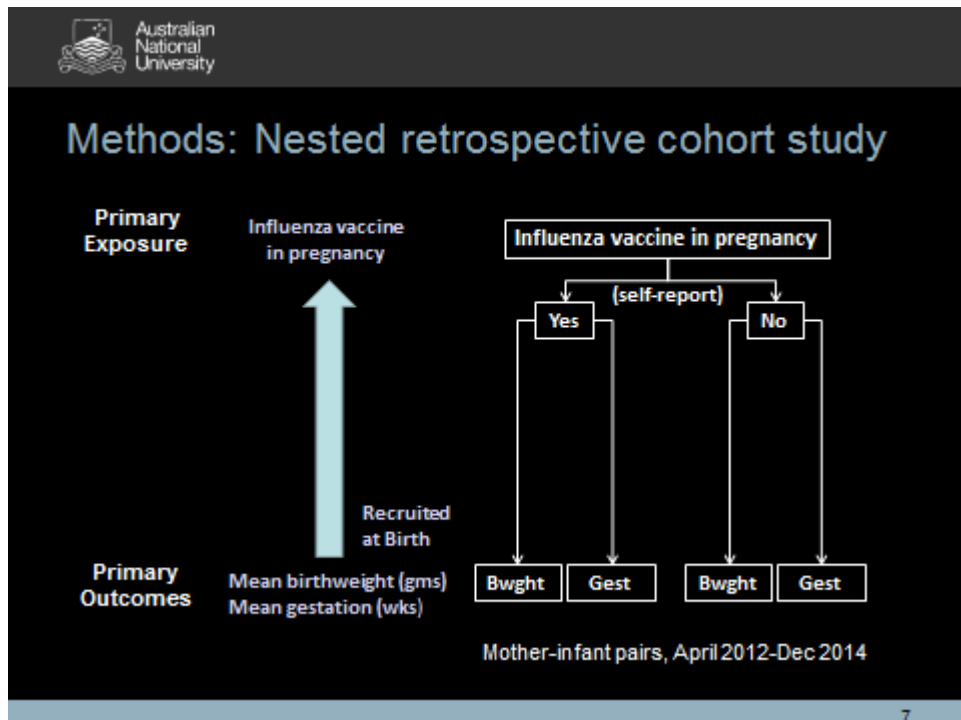
Australian National University

Results: Baseline characteristics

Table 1 FluMum study participants, by self-reported maternal influenza vaccine in pregnancy status, Australia (2012-2014)

Variable	Influenza vaccine in pregnancy (self-reported)		Total participants
	Yes n=2394	**No** n=4732	**n=7125**
Maternal age (mean, in years)	32.1	31.5	31.7
Mother Aboriginal and/or Torres Strait Islander	75/2393 (3%)	128/4725 (2%)	203/7118 (3%)
Wks pregnant 1st antenatal care	8.2 weeks	8.8 weeks	8.6 weeks
Smoking in pregnancy	141/2392 (6%)	383/4726 (8%)	524/7118 (7%)
Diabetes in pregnancy	229/2391 (10%)	364/4724 (8%)	589/71157 (8%)
Any co-morbidity/flu risk factor	558/2393 (23%)	969/4726 (21%)	1527/7119 (21%)

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Australian National University

Results: Baseline characteristics

Table 1 FluMum study participants, by self-reported maternal influenza vaccine in pregnancy status, Australia (2012-2014)

Variable	Influenza vaccine in pregnancy (self-reported)	
	Yes n=2394	**No** n=4732
Maternal age (mean, in years)	32.1	31.5
Mother Aboriginal and/or Torres Strait Islander	(3%)	(2%)
Wks pregnant 1st antenatal care	8.2 weeks	8.8 weeks
Smoking in pregnancy	(6%)	(8%)
Diabetes in pregnancy	(10%)	(8%)
Any co-morbidity/flu risk factor	(23%)	(21%)

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3.   Data analysis: Laboratory Confirmed Pertussis Notifications in Queensland 1997-2014

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Prologue

Background

It is known notification data are generally not used for analytical assumptions but rather as an indication of how effective a surveillance system is operating or for quality assurance purposes. They provide important opportunities to observe trends and responses to interventions such as immunisation programs. Pertussis has been a notifiable disease in Queensland since 1997.The aim of this project was to present a case series analysis of all pertussis notifications in Queensland since this date.

My role

I conducted all of the data analysis required of this project. This included; applying and acquiring ethics approvals, designing a data analysis plan, preparing the data by cleaning and coding in a Stata do-file as well as all data analyses. I also merged two major datasets and calculated rates as well as construct graphs to present the results.

Lessons learned

Rates, rates, rates. I never knew how much time was involved in calculating average annual notification rates by year of notification or age or sex. I also learned a great deal about presenting data in this project. After generating so many results from so much data I found it challenging to determine which data to present and how. It was also a learning experience merging two Stata do-files. Learning how to achieve this in courseblock was quite different to putting it into practice in a real life scenario. This was fun, gratifying and challenging.

Public Health Impact

Pertussis remains endemic in most parts of the world and continues to be difficult to control. In these analyses, infants under 6 months of age recorded the highest notification rates of 196.5 per 100,000 populations. Rates declined sharply once infants reached over 12 months of age. There is evidence suggesting maternal pertussis vaccination administered during the last trimester of pregnancy has a protective effect in infants in the first few months of life. It will be worth observing the data that arises from the Queensland maternal pertussis vaccination program which commenced on 01 August 2014 regarding pertussis notifications in infants less than four months of age.

Abstract

Introduction

Pertussis is a highly contagious disease which has epidemic cycles. Outbreaks occur regularly every three to four years with varying degrees of severity.Treatment of pertussis is based on clinical findings and diagnosis and control is a high public health priority. Morbidity and mortality is highest in infants under six months of age and control efforts focus on preventing disease in this age group by minimizing exposure by other infected cases. Despite ongoing immunisation programs, pertussis was the most commonly reported vaccine preventable disease (VPD) in Australia in 2010 and accounted for over half of all VPD notifications. The aim of this project was to present case series analysis of all pertussis notifications in Queensland since this date.

Methods

I conducted a retrospective case series analysis of all notified cases of pertussis occurring in Queensland from 01 January 1997 to 31 December 2014. This was achieved by extraction of all valid (laboratory confirmed) and probable (clinical) notified cases of pertussis in Queensland according to the current case definition. Descriptive epidemiology and temporal trends of pertussis notifications in Queensland over time were examined. Results are presented as baseline demographic characteristics and summary statistics in the form of proportions, counts and average annual rates, by year of notification, age and sex.

Results

There were 53,901 unique notified laboratory confirmed pertussis cases and 46,998 laboratory testing results examined. Over the 18 year observation period (1997-2014), the median age of persons notified with pertussis was 35.2 years. There were more females compared to males for each year of notification and an over representation of Aboriginal and Torres Strait Islander persons (10%) – albeit with proportion of records (69%) with missing data on Indigenous status. Amongst children less than three years of age, notifications of pertussis were most common amongst the youngest infants, that is those <4 months of age. The highest number of notifications recorded for a single year was in 2011 with 8,984 cases and the lowest number of notifications occurred in 2000 with 537 cases. Serology (66%) and PCR (33%) were the most

common test types for confirmation of a diagnosis with only 1% culture. The increase in pertussis notifications from 2009 coincided with a substantial increase in the number of cases diagnosed by PCR.

Conclusions

The results in this case series for notifications of pertussis by age are consistent with that of overseas literature. It will important to monitor the outcomes of the implementation of the Queensland maternal pertussis vaccination program which commenced on 01 August 2014 regarding pertussis notifications in infants less than four months of age.

Introduction

Bordetella pertussis is a bacterial, vaccine-preventable infectious disease causing a condition known as 'pertussis' or 'whooping cough'.[1] Pertussis is a highly contagious disease, particularly in the first two weeks, that can result in significant morbidity and mortality.[1] The incubation period ranges from 6-20 days with an average of 9-10 days.[1] According to the World Health Organization (WHO), global immunisation coverage of infants in 2014 who had received all three doses of pertussis vaccine was estimated at 86%.[2] In Australia this was greater than 90%.[2] In 2010, pertussis was the most commonly reported vaccine preventable disease (VPD) in Australia and accounted for over 50% of all VPD notifications.[3]

Pertussis is a disease that has epidemic cycles.[4] Outbreaks occur regularly every three to four years with varying degrees of severity, despite ongoing immunisation programs. Those that acquire pertussis and are unvaccinated or only partially vaccinated have higher degrees of morbidity and mortality,[5] particularly infants under six months of age. Disease severity is high in this age group with case fatality rates reportedly 1 in 200 infants.[6] The epidemiology of pertussis in Australia shows a similar pattern.[7] Generally, the most likely mode of transmission of pertussis is from exposure to other household members who are infected; particularly mothers, fathers and grandparents, followed by siblings, as well as exposure to children in child care and other health care settings.[8] In the 2008-2012 pertussis epidemic in Perth, siblings were identified as being the highest source of infection to infants under six months of age, which was thought to be due to waning immunity amongst these siblings.[9]

Treatment of pertussis is based on clinical findings and diagnosis. Control of pertussis is a high public health priority, with control efforts focusing on preventing disease in children under 6 months of age, particularly by minimizing exposure to this age group by other infected cases.[10]

Pertussis is a nationally notifiable disease and has been a notifiable disease in Queensland since 1997. Clinicians and laboratories are required to notify public health units (PHU) within one working day of probable and confirmed diagnoses. The Queensland Notifiable and Other Conditions System (NOCS) records all notifications of

pertussis received from laboratories and clinicians. Public health units access these data for public health follow up. The NOCS system is a source of information regarding the incidence and prevalence of pertussis in Queensland and can provide information on disease acquisition, morbidity and mortality on the cases that are followed up by a PHU. Information assists in planning of Queensland's Health (QH) services and is used for national and state reporting. De-identified notification data are forwarded to the Australian National Notifiable Disease Surveillance System (NNDSS).

The primary aim of this project was to present descriptive epidemiological results of all notified cases of pertussis occurring in Queensland from 01 January 1997 to 31 December 2014. To achieve this, the primary objective was to perform a descriptive case series analysis of these data by extraction of all valid (laboratory confirmed) and probable (clinical) notified cases of pertussis in Queensland.

Methods

Study design and population

The study design for this data analysis project was a retrospective case series. The study population was formed using the population hierarchy shown in Figure 3.1. Here the source population was all cases of pertussis that occurred in Queensland from 1997-2014, whereas the database population was limited to those cases of pertussis notified to a public health unit by a clinician or laboratory. The database population did not capture those cases of pertussis who did not present to a health care provider or were not notified to the public health authority by a health care provider/diagnostic laboratory. Notified cases of pertussis were entered into the NOCS system as being either valid or probable cases. This database population also included notifications that were later found to have not met the case definition (see below) or were duplicates which were removed. Following data cleaning, the study population was formed and became the final dataset, of which data in this project were analysed.

Figure 3.1:   Population hierarchy for laboratory confirmed pertussis data analysis, Queensland 1997-2014.
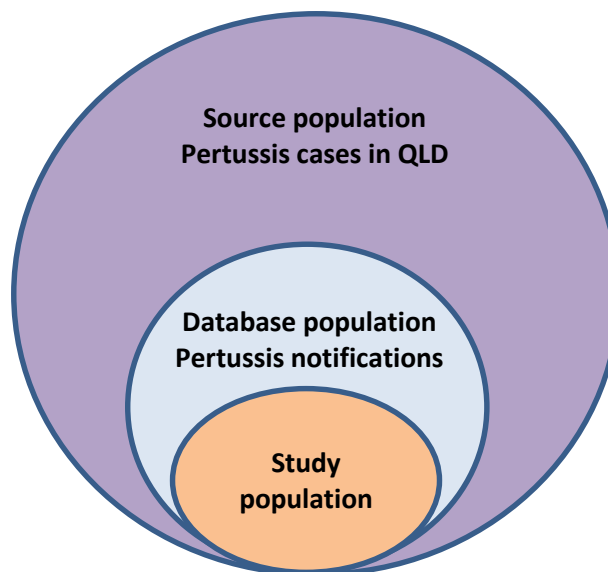
Case definition

The NNDSS case definition for pertussis was implemented by Communicable Diseases Network Australia (CDNA) in February 2009. Revisions in January 2013 and April 2015,[11] included components related to case management, follow-up of contacts, revision of the mechanism of transmission and antibiotic use. None of these revisions by CDNA affected the way a case was classified as probable or confirmed for these data analyses.

The current national case definition for pertussis recommends both probable and confirmed cases should be notified. Guidance for reporting cases includes the consideration of laboratory, clinical and epidemiological evidence as outlined in Figure 3.2 below. The case definition was used in preparation of data cleaning prior to analysis of the pertussis notifications.

Figure 3.2: **Matrix for reporting pertussis notifications using National Notifiable Disease Surveillance System case definition, 01 July 2013.**

Confirmed case

-laboratory

definitive evidence

OR

-laboratory

suggestive evidence

AND clinical

evidence.

Probable case

-clinical **AND** epidemiological evidence required.

Laboratory definitive evidence
-isolation of Bordetella pertussis **OR**
-detection of *B. pertussis* by nucleic acid testing **OR**
-Seroconversion in paired sera for *B. pertussis* using whole cell or specific *B. pertussis* antigen(s) in the absence of recent pertussis vaccination.

Laboratory suggested evidence

In the absence of recent vaccination
-significant change (increase or decrease) in antibody level (IgG, IgA) to *B. pertussis* whole cell or *B. pertussis* specific antigen(s) **OR**
-Single high IgG and/or IgA titre to Pertussis Toxin (PT) **OR**

-Single high IgA titre to Whole Cell *B. pertussis* antigen.

Epidemiological evidence (link established when there is)

-Contact between two people involving a plausible mode of transmission at a time

when:

-one of them is likely to be infectious (from the catarrhal stage, approximately one week before, to three weeks after onset of cough) **AND**
-the other has an illness which starts within 6 to 20 days after this contact **AND**
-at least one case in the chain of epidemiologically linked cases (which may

involve many cases) is a confirmed case with either laboratory definitive or

laboratory suggestive evidence.

Data extraction

De-identified data were extracted from the Queensland NOCS database by senior data managers of the Communicable Diseases Branch (CDB), Queensland Government Department of Health. These data were then made available to me electronically in the form of a password protected Microsoft Excel spreadsheet containing two separate spreadsheets; one containing demographic characteristics and the other laboratory confirmed cases of pertussis from 01 January 1997- 31 December 2014. Stata v.12 (StataCorp, Texas, USA) was the statistical software package used to complete all analyses.

The extracted data included all valid (laboratory confirmed) and probable (clinical and epidemiological) cases of pertussis according to the Australian National Notifiable Disease Surveillance System (NNDSS) case definition.[11]

Study variables

Table 3.1 contains the demographic characteristics and laboratory notification variables included in the pertussis data analysis. These variables were pre-existing data fields in the NOCS database specified in the ethics application.

Table 3.1:   **Study variables included in pertussis data extraction for proposed analysis.**

Demographic characteristics variables	Laboratory notification variables
Notification reference number* ⟷ Notification reference number*	Notification reference number*
Person reference number	Date of onset of illness
Date of birth	Laboratory name
Notification date	Specimen
Date of onset of illness	Collection date
Diagnosis date	Test ID
Age at onset of illness	Test type
Sex	Result
Indigenous status †	Organism
Public health unit	
Died of condition	
Deceased date	
Validity	
Number of lab tests performed	

* Unique identifier used for merging of the two datasets, † People who identified as being of Aboriginal and or Torres Strait Islander origin.

Data cleaning

Variables were examined individually for logic, whilst missing data were coded as such. Data cleaning, recoding, labelling and final analyses were all conducted using a do-file that I wrote in the statistical data analysis package Stata version 12.1 (Appendix 3.1).

Cases were excluded that showed negative ages in years at onset of illness. These negative ages in the dataset were unable to be clarified, validated or corrected due to the nature of the project and the length of time since original data collection.

The number of days from the onset of illness to notification date were calculated but were not utilised for the purposes of analysis due to substantial inconsistencies in the variable generated resulting in illogical numbers of days in some circumstances. For the vast majority of records where an onset of illness date was included, this was the same date as the notification date. Therefore the recorded onset of illness date was considered unreliable and was not included in the analysis. The variables 'Organism', 'Serogroup', 'Serotype' and 'Subtype' contained no data and were therefore excluded.

The 'notification reference number' variable was used as the unique study identifier to merge the two Microsoft Excel datasets (clinical and laboratory) and then the data were examined for duplicate entries. Duplicate results that were identified were subsequently deleted by recoding in the Stata do-file.

Analysis

Statistical methods

Age in years at the date of notification was recorded in the NOCS database as a continuous variable, from which age groups were created. Following data cleaning, remaining string variables were recoded as categorical or binary and dates formatted into DMY.

As the data were not normally distributed, the median age rather than mean age were calculated for the various age strata. Age-specific notification rates were calculated for all age groups using Australian Bureau of Statistics' estimated Queensland resident population data as the denominator.[12] For children less than three years old, where disease severity is high, age-specific notification rates were also calculated for age groups; 0-<6months, 6-<12months and 1-3 year olds. Age groups for all ages were created in Stata then exported to a Microsoft Excel worksheet to calculate average annual notification rates per 100,000 total populations for each age group.

Descriptive epidemiology and temporal trends of pertussis notifications in Queensland over time were examined. Results are presented as baseline demographic characteristics and summary statistics in the form of proportions, counts and average annual rates, by year of notification, age and sex. Graphs and figures were created in Stata v12.1 and Microsoft Excel.

Ethics approval

Unconditional ethics approval was received for this data analysis project by the Human Research Ethics Committee of Queensland Department of Health approval number HREC/14/QRCH/367. Research Governance authorisation was also obtained from Queensland Health.

Results

Study population

There were 53,944 pertussis notifications recorded as confirmed and 82,247 laboratory test entries extracted from the NOCS database from 01 January 1997 to 31 December 2014. There were 22 cases where dates of birth were illogical due to data entry error. These resulted in negative ages and were excluded. Once the two datasets were merged and cleaned, there were 53,901 unique notified laboratory confirmed pertussis cases and 46,998 laboratory testing results (Figure 3.3). There were 43 duplicate entries found in the notification dataset which were subsequently deleted. There were multiple laboratory entries found for some cases and these were managed in the analysis by coding in the Stata do-file. Notifications were managed by ten of the public health units (PHU) within Queensland. Metropolitan South PHU recorded the most notifications over the period with 12,740 (24%) individual cases (Table 3.2).

Figure 3.3:   **Final study population from merger and cleaning of clinical and laboratory datasets for pertussis notifications, Queensland, 1997-2014.**

```
┌─────────────────────────┐
│   Clinical dataset      │
│  53,944 notifications   │
└─────────────────────────┘
             │
             │     ┌──────────────────────────────┐
             └─────│  Merged with laboratory dataset│
                   │       82,247 records           │
                   └──────────────────────────────┘
                              │
                              │      ┌───────────────────────────────────┐
                              ├──────│  43 duplicate notifications excluded│
                              │      └───────────────────────────────────┘
                   ┌──────────────────────────────┐
                   │  22 excluded for date of birth errors│
                   │       (negative age years)    │
                   └──────────────────────────────┘
                              │
                              │      ┌───────────────────────────────────┐
                              └──────│  Clinical and laboratory dataset    │
                                     │  53,901 unique notification records │
                                     └───────────────────────────────────┘
```
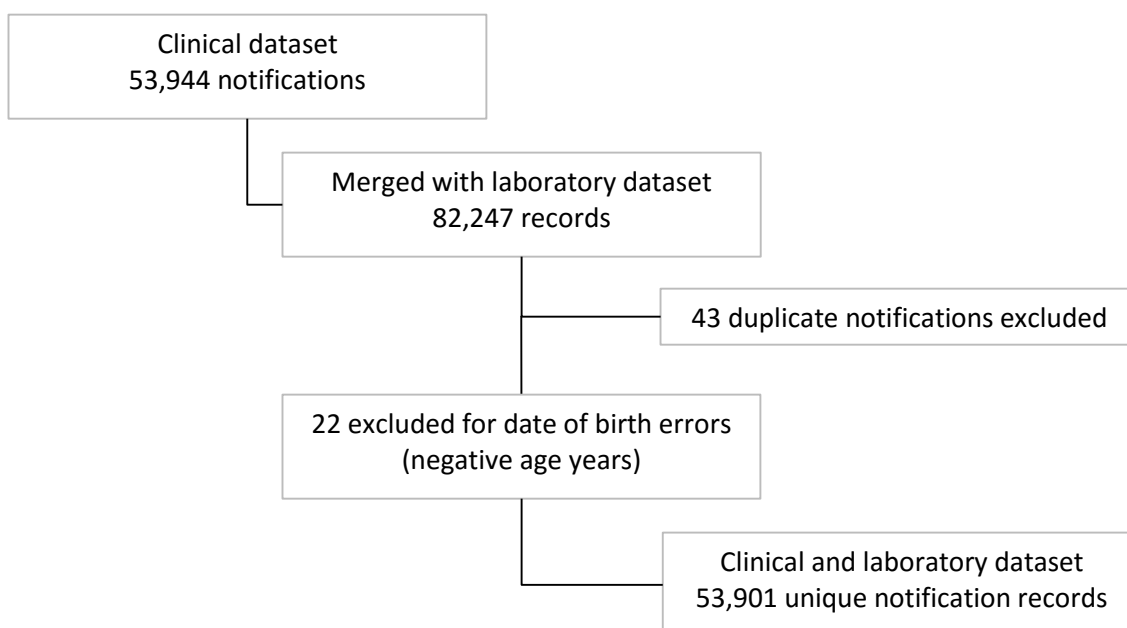
Most notifications occurred in the month of November (11 %). The range for other months was 7-10% with April recording the lowest percentage of notifications at 6%.

Baseline characteristics of study population

Over the 18 year observation period (1997-2014), the median age of persons notified with pertussis was 35.2 years, most (56%) were female and there was an over representation of Aboriginal and Torres Strait Islander persons (10%) – albeit with a very large proportion of records (69%) with missing data on Indigenous status (Table 3.2). All of the notifications in the final dataset had an accompanying record of laboratory confirmation consistent with the case definition.

The number of pertussis notifications rose markedly in 2009 (Figure 3.4) and remained elevated until 2013 when notifications began to decline. The highest number of notifications recorded for a single year was in 2011 with 8,984 cases and the lowest number of notifications occurred in 2000 with 537 cases. There were more females compared to males for each year of notification (Figure 3.5) and across almost all age groups when expressed as age-specific rates (Figure 3.6).

Table 3.2:   **Baseline characteristics of laboratory confirmed pertussis cases Queensland, Australia (1997-2014).**

Characteristics	Total cases N= 53,901 (%)
Age, median in years (range)	35.2 (<1-99)
Sex Males	23,864 (44%)
Indigenous status *	**N= 16,454** 1,632 (10%)
Public Health Units (PHU's) Metro South PHU Metro North PHU Sunshine Coast PHU Gold Coast PHU Darling Downs PHU Townsville PHU Cairns PHU West Moreton PHU Rockhampton PHU Wide Bay PHU	**N= 53,799** 12,740 (24%) 11,029 (20%) 5,121 (10%) 4,998 (9%) 4,915 (9%) 4,331 (8%) 3185 (6%) 3126 (6%) 2305 (4%) 2049 (4%)

* People who identified as being of Aboriginal and or Torres Strait Islander origin.

Figure 3.4:   **Epidemiologic curve showing individual laboratory confirmed notified cases of pertussis notified in Queensland, 1997-2014.**
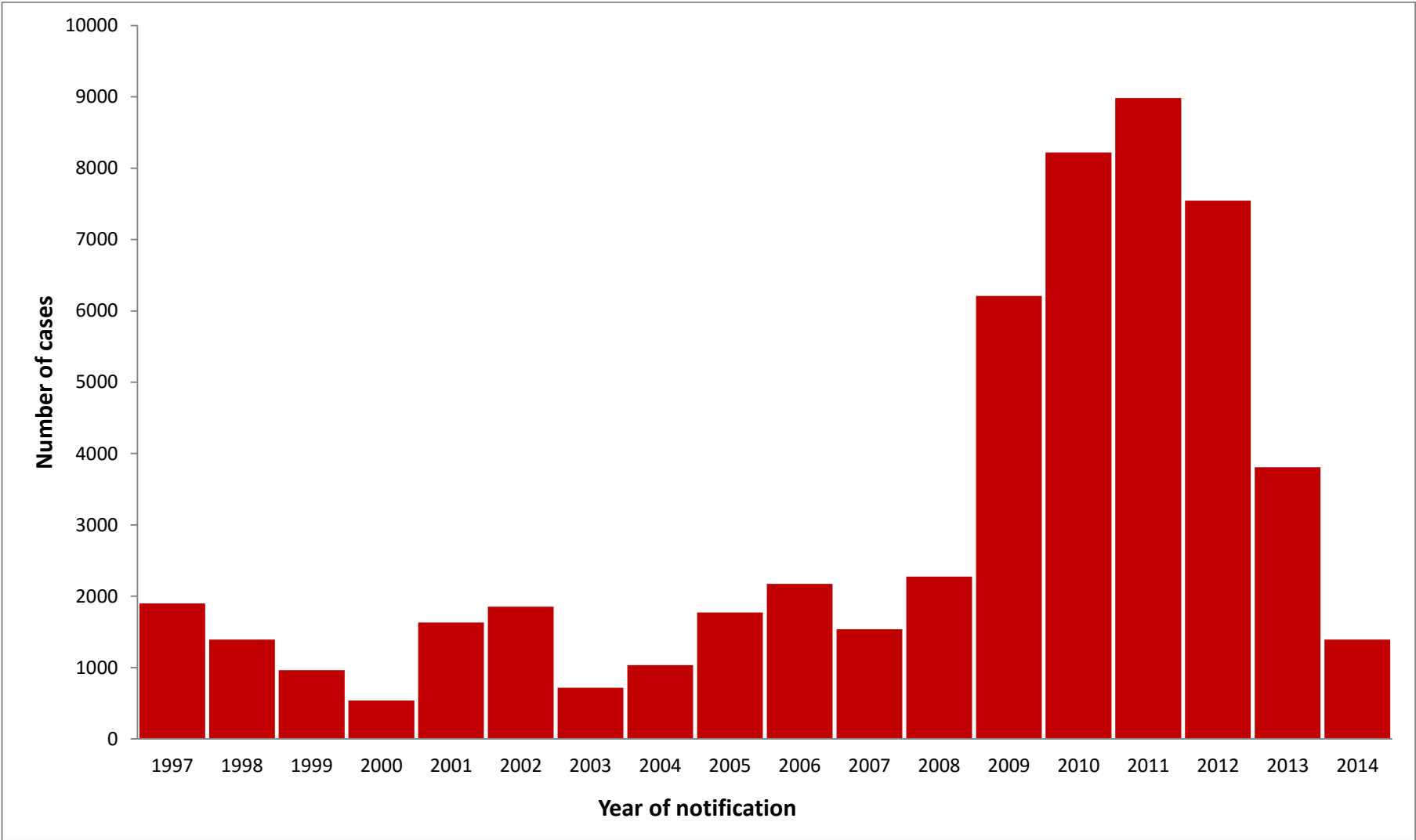
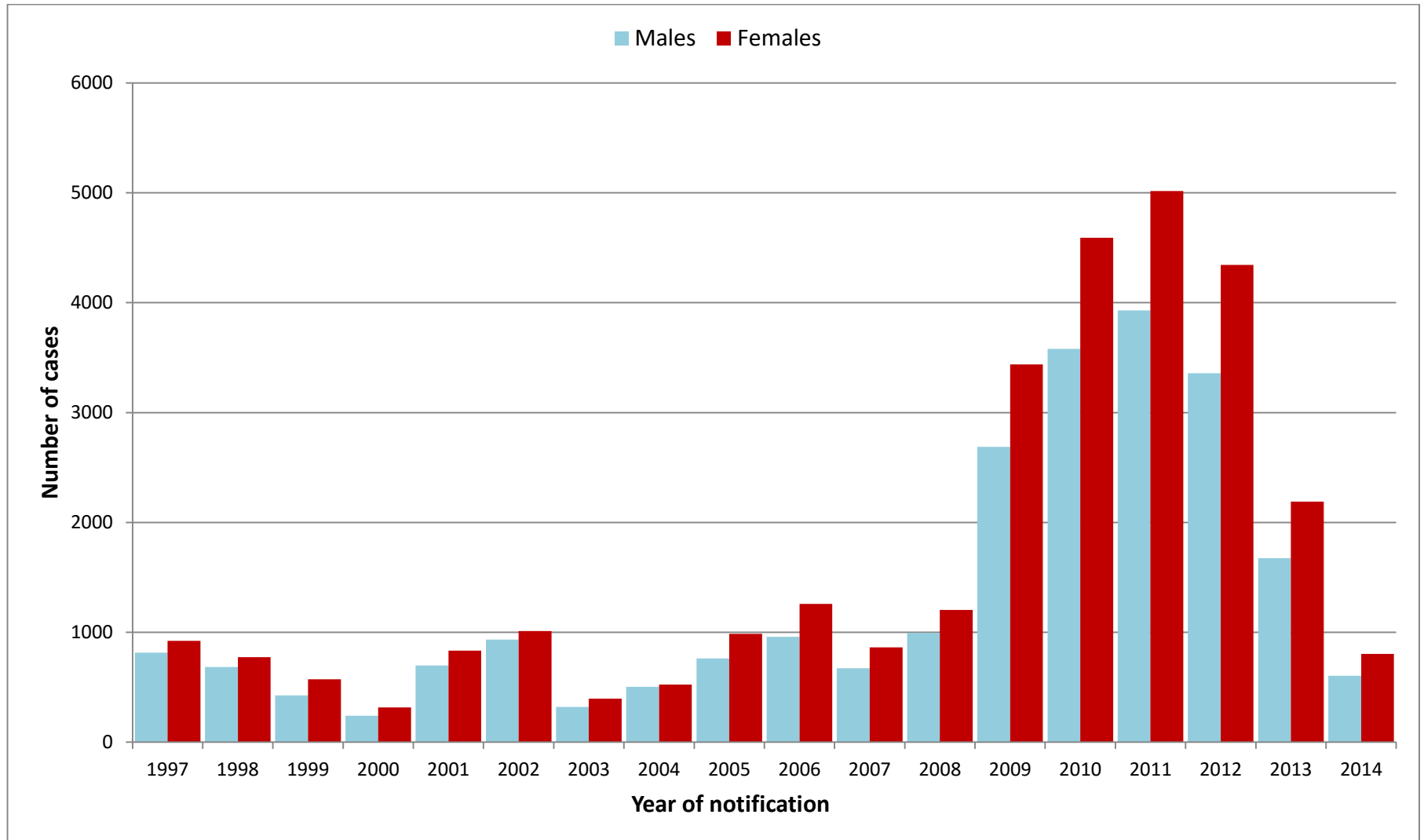**Figure 3.5:   Pertussis notifications in Queensland by year and sex, 1997-2014**
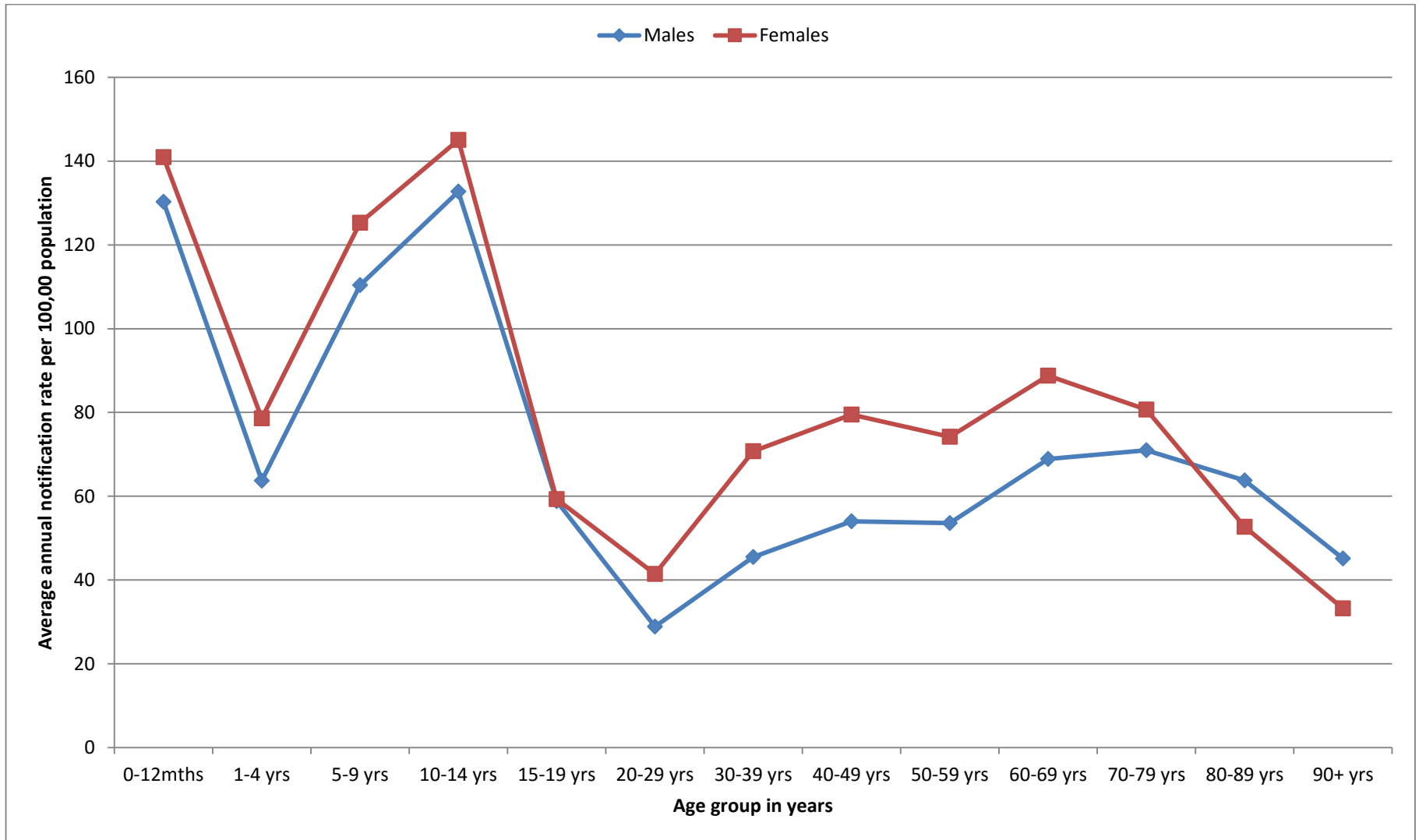
Figure 3.6:   Average annual pertussis notification rates per 100,000 population in Queensland by age and sex, 1997-2014

Infants and Children

Amongst children less than three years of age, notifications of pertussis were most common amongst the youngest infants, in particular those <4 months of age (Figure 3.7). The average annual age-specific notification rates over the period from 1997-2014 were highest amongst infants under 6 months, 196.5 per 100,000 population (Table 3.3). This age-group also had the highest age-specific notification rates throughout the period of observation peaking in 2002, 2005 and 2010-2011 consistent with epidemic cycles (Figure 3.8).

Table 3.3:   **Baseline characteristics and rates of 2,911 children <3 years, with laboratory confirmed pertussis in Queensland, 1997-2014**

Characteristics	Infants <6months	Infants 6-<12 months	Children 1yr-<3yrs
N (%)	**1,009 (35%)**	**392 (13%)**	**1,510 (52%)**
Notification rate per 100,000 population*	196.5	74.7	47.4
Sex Male	494 (49%)	199 (51%)	684 (45%)
Indigenous Status†	163 (21%)	48 (19%)	104 (11%)
Deaths‡	6 (100%)	0	0

* Average annual notification rates 1997-2014

† Infants who have been identified as being Aboriginal and/or Torres Strait Islander

‡ Deaths as a direct result of pertussis infection

The average annual age specific notification rates for all age-groups (Figure 3.9) show the same epidemic cycle evident amongst the youngest children (Figure 3.8) with peaks in notification rates in 2001-2002, 2005-2006, and 2009-2012. Of note, the period coinciding with the most recent epidemic period is on top of a much higher baseline (Figure 3.9).

Figure 3.7: **Confirmed cases of pertussis in Queensland children less than 3 years, 1997-2014**
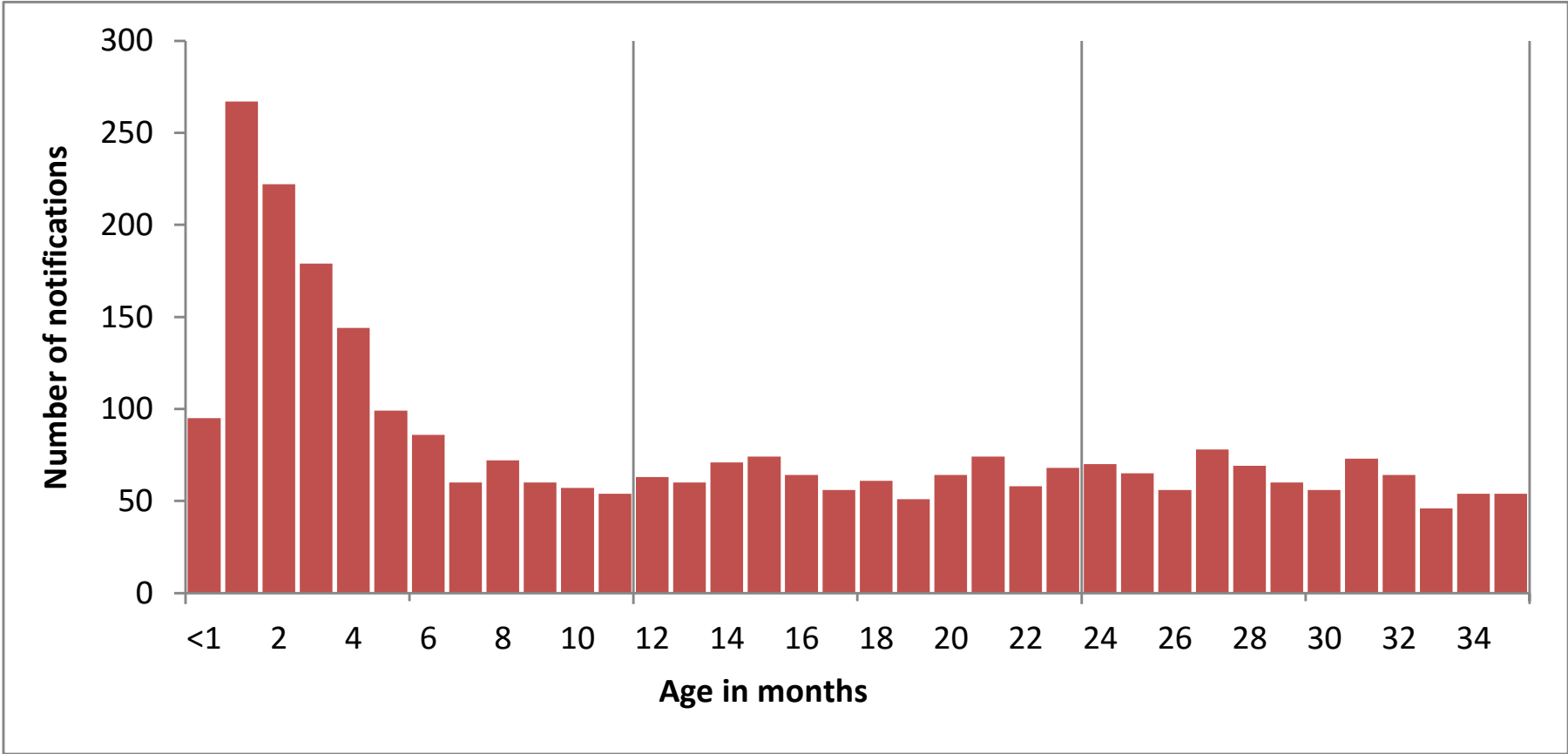
Figure 3.8: Age specific notification rates of laboratory confirmed pertussis in children under 3 years per 100,000 population, Queensland, 1997-2014.
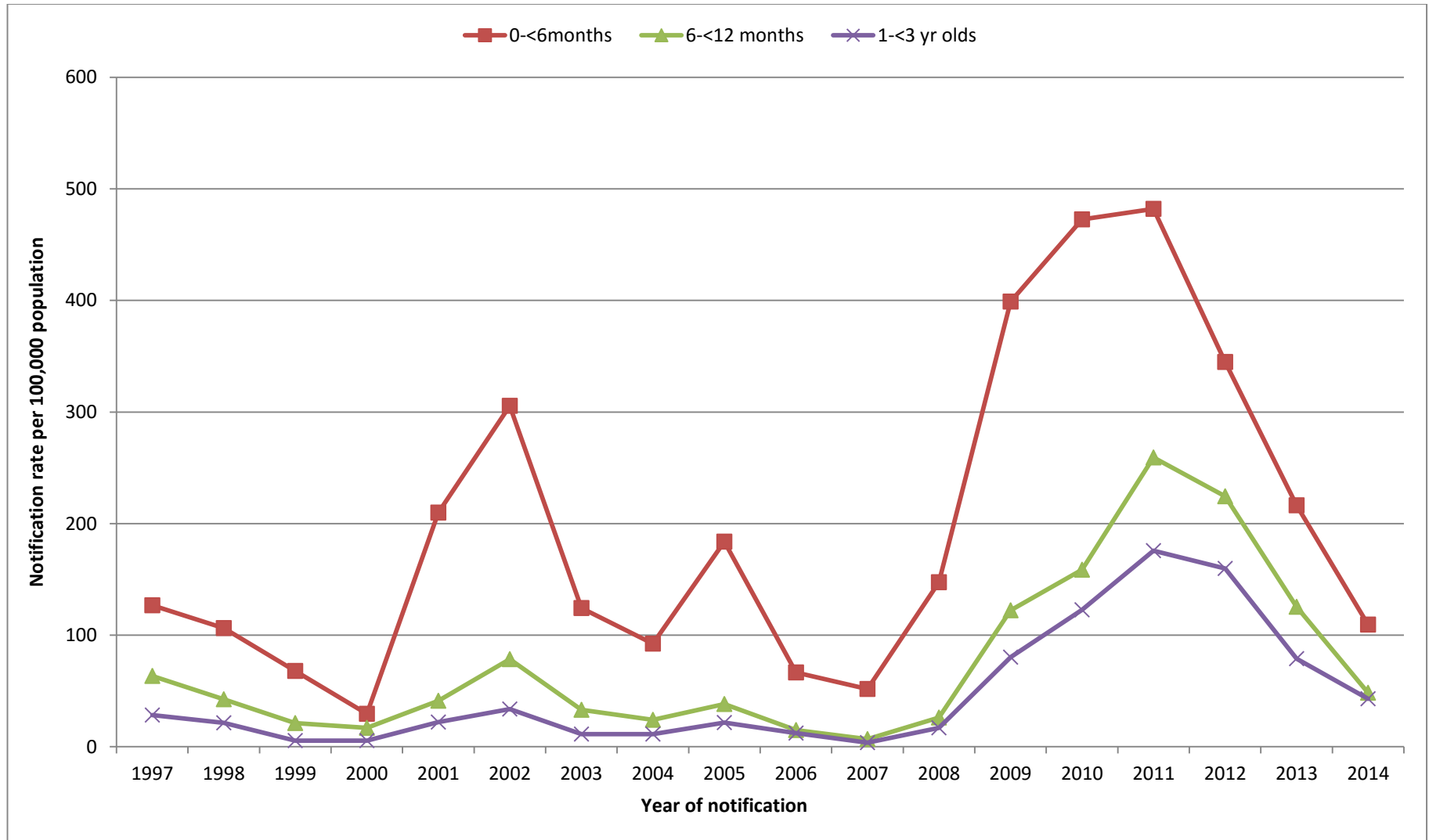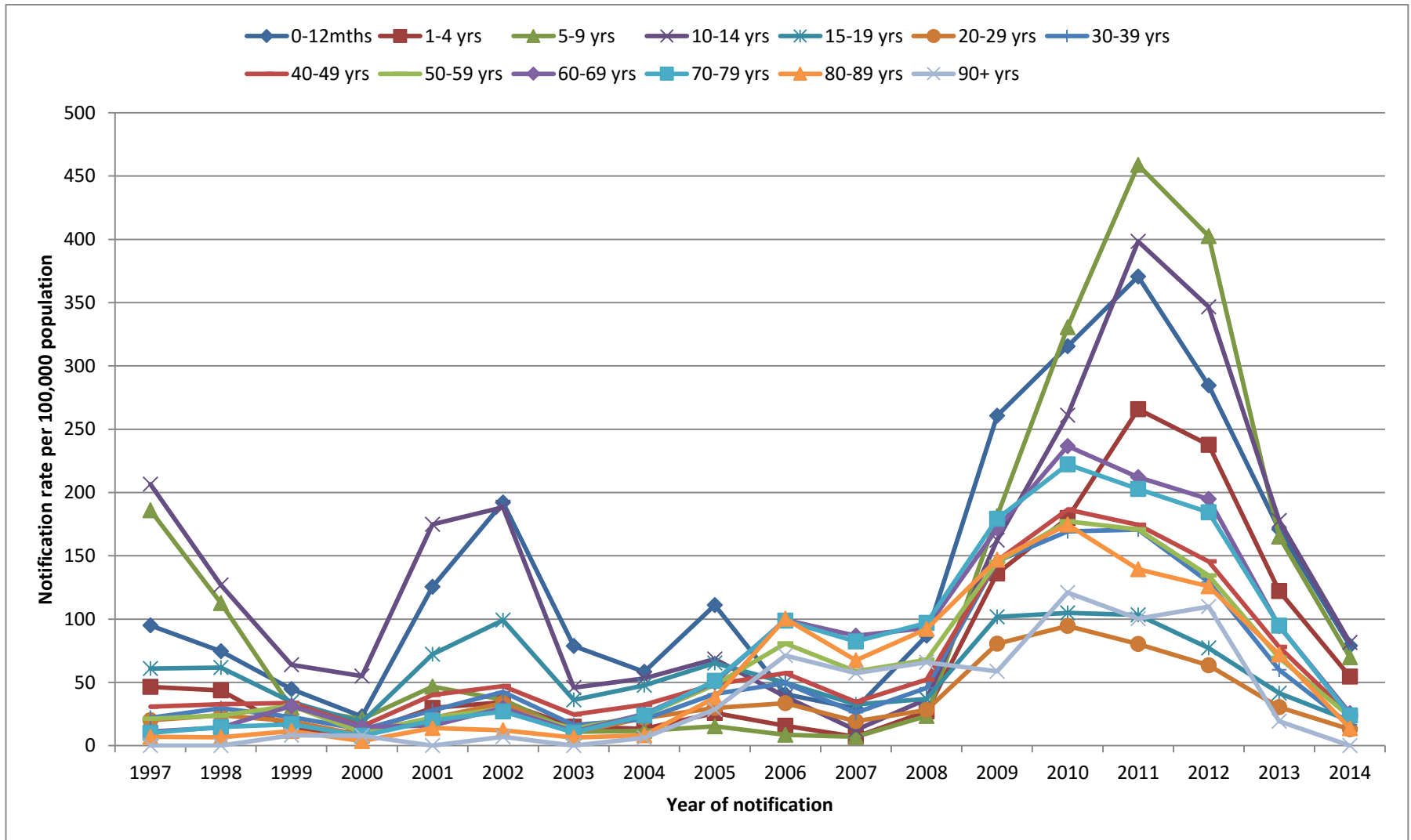
Figure 3.9:   **Average annual notification rates of Pertussis in Queensland by year of notification and age group, 1997-2014**

Laboratory

Of 46,998 specimens obtained for confirmation of diagnosis of pertussis, most (65%) were blood samples, 30% were swabs of unknown origin, whilst nasopharyngeal aspirate (NPA) (4%) was the most common of the remainder (Table 3.4). There were no testing data available from 1997-2000. Of 49,145 individual results where the test type was known, serology (66%) and polymerase chain reaction (PCR) (33%) were the most common test types for confirmation of a diagnosis with only 1% culture. The increase in pertussis notifications from 2009 coincided with a substantial increase in the number of cases diagnosed by PCR (Figure 3.10).

Table 3.4:   Specimen types and test types of laboratory confirmed pertussis positive cases Queensland, Australia (1997-2014).

Specimen type	N= 46,998
Blood sample	30, 5084 (65%)
Swab-undefined	14,012 (30%)
NPA	1,971 (4%)
Sputum	67 (0.1%)
Bronchial lavage	6 (0.1%)
Urine	1 (0.1%)
Faeces	7 (0.1%)
Other	426 (0.1%)
Confirmation of diagnosis by test type	**N= 49,145**
Serology positive	32,522 (66%)
PCR	16,120 (33%)
Culture	468 (1%)
Other positive test	35 (0%)

Figure 3.10:   Pertussis notifications in Queensland by test type, 1997-2014
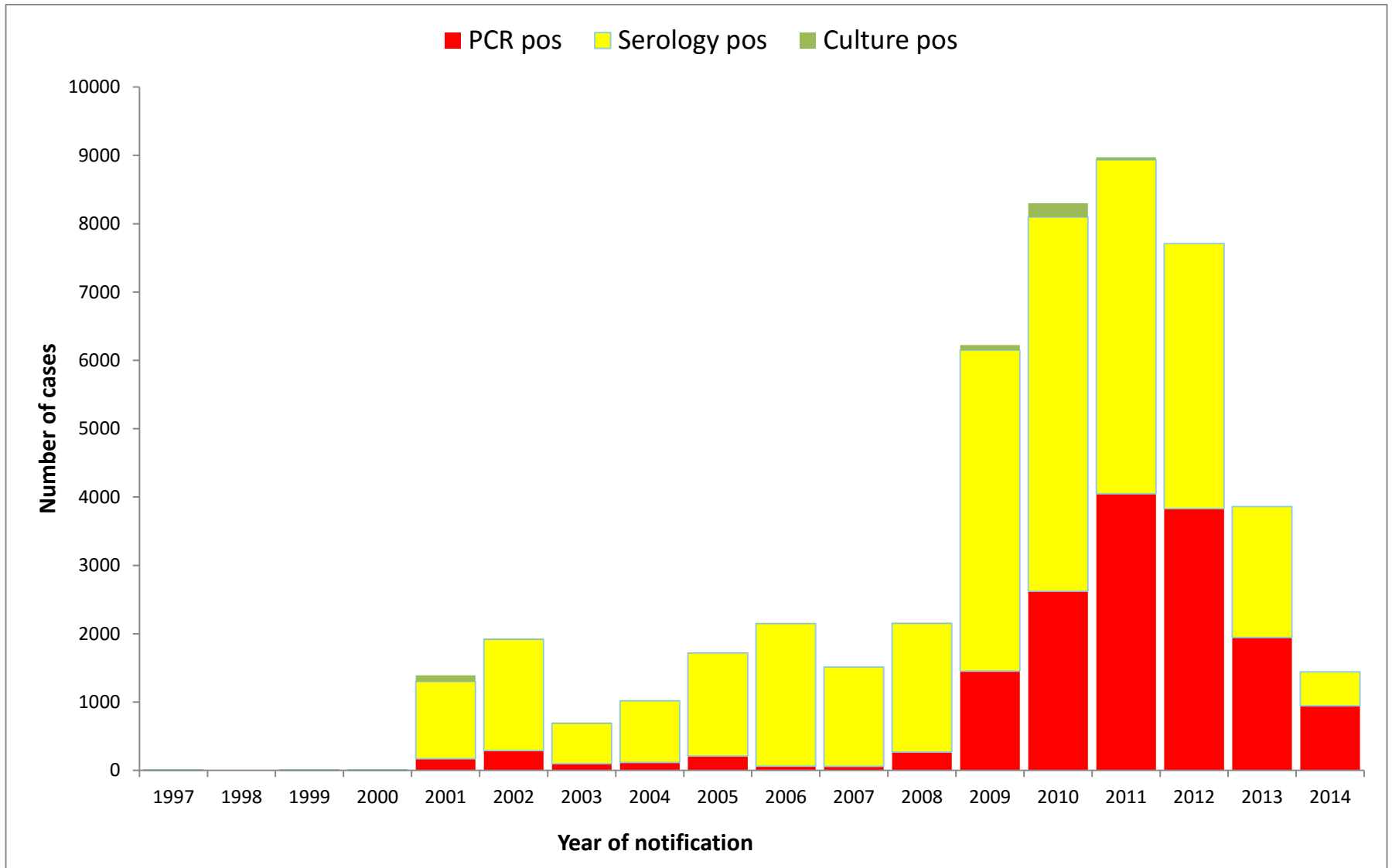
Test type by age groups

There were no testing data available from 1997-2000. Test type from 2001-2007 was predominantly PCR for the 0-12 month and 1-4 years age groups, and predominantly IgA (serology) for the remaining age groups (Figure 3.11). Testing type from 2008-2014 showed an increase in PCR in all age groups under 15 years, and an increasing trend of PCR use for testing in all remaining age groups (Figure 3.12).

Deaths

Whilst death due to a notifiable condition is itself not notifiable, there were six deaths in total directly related to pertussis infection recorded in NOCS. All deaths occurred in infants under six months of age and one child was identified as being of Aboriginal or Torres Strait Islander origin. There were 5 male infants (83%) and one female infant. There were two deaths in 2001, two in 2002, one in 2005 and one in 2012. Geographically, two deaths occurred in the South East area of Queensland in separate years, two deaths in Far North Queensland in different years, one death in the Darling Downs area and one death in the West Moreton region.

Test type by age groups

Figure 3.11: **Type of test for diagnosis of pertussis by age group, Queensland 2001-2007**
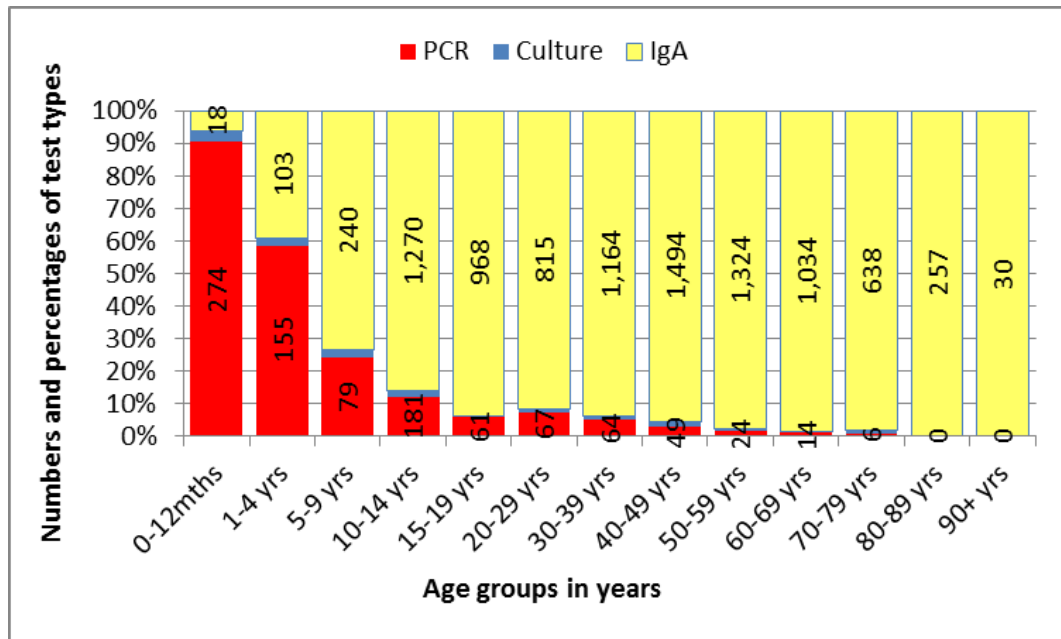
NB: Other N=35 excluded

Figure 3.12: **Type of test for diagnosis of pertussis by age group, Queensland 2008-2014**
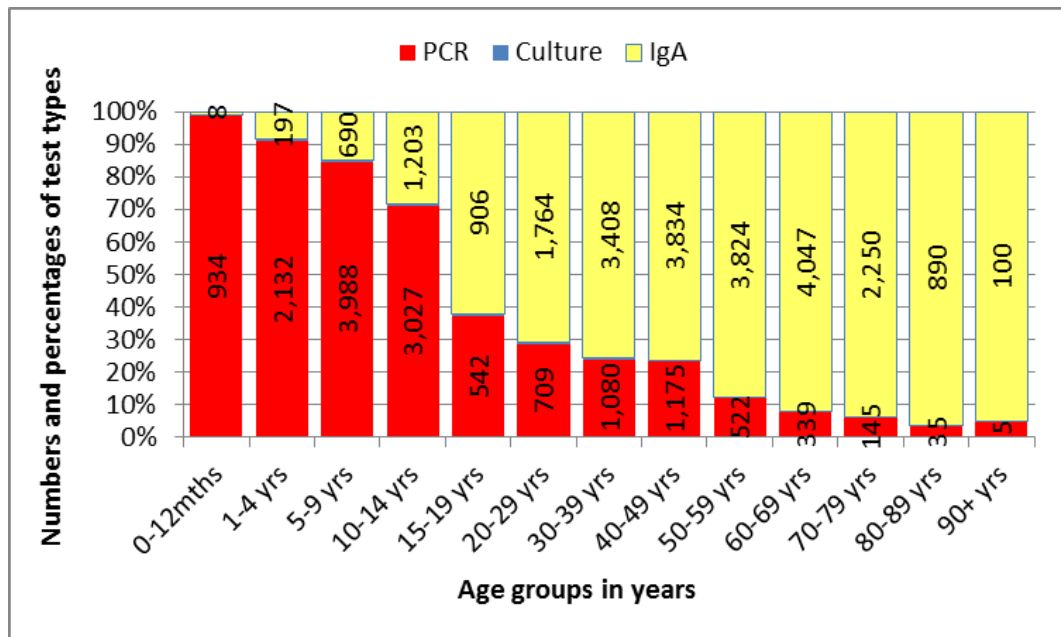
NB: Other N=35 excluded

Discussion

Notifications for pertussis in Queensland rose markedly from 2009-2012. Outbreaks of pertussis occur regularly in Australia[8] and there were increases in notification rates nationally during this time period.[3] Australian Bureau of Statistics data for communicable diseases in 2010 showed pertussis was the most commonly notified VPD accounting for 56% of total VPD notifications.[3]

There were more laboratory confirmed pertussis notifications in females compared to males in all age categories apart from the infants in the 6-12 month age group. The current literature reports pertussis incidence, morbidity and mortality are all higher in females than males,[5] and this is consistent with these data apart from mortality. In Queensland, five out of the six deaths that were identified over this period as being directly as a result of pertussis infection were male infants and all of the deaths occurred in children under six months of age. This is an age at which infants are particularly vulnerable to severe outcomes from pertussis infections, especially if unvaccinated or have not yet received all the recommended scheduled doses of the vaccine.[5]

Interpretation

In Queensland, three major pathology providers service more than 90% of the market. All three providers notify electronically, resulting in efficient and timely notification of laboratory notifiable conditions. Notification data in this report are presented based on the population health case definitions in use over the period as described in the Queensland Health Disease Control Manual (Notifiable diseases report 2002-2006) and the Australian NNDSS surveillance case definition.[11] Available national notification data for pertussis for the years 2006-2012 showed Queensland notifications were slightly higher to those nationally.[13] This increase in Queensland notifications may be due in part to the type of laboratory testing used.

Average annual notification rates

The highest average annual notification rates across all age groups were in those under 6 months of age, which was most evident during epidemic peaks and is consistent with

the international literature.[14] Whilst age-specific notification rates increased for all age groups from 2009, school-aged children (those aged 5-14 years) were particularly high.

I found no evidence of seasonality in pertussis notification data with only a very narrow range of differences in percentages by month of notification. Most notifications were reported in the month of November (11%), with remaining months recording similar percentages (range 7-10%). April recorded the lowest number of notifications at 6%. Others, using Queensland notification and laboratory testing data from 2008 and 2011, have been able to show that the notification data masks testing trends. The authors found by having access to all tests undertaken rather than just those found to be positive that both the proportion of PCR tests that were positive and the proportion of serology tests that were positive both provided evidence that pertussis is a seasonal illness in Queensland with annual peaks in the summer months.[15]

Laboratory testing

PCR use has increased as the testing type for pertussis infections over time which may have led to increased detection of cases.[16] From 2008-2014 these data showed an increasing trend in PCR testing in all age groups however this was a sustained epidemic period and this increased trend in testing is possibly a result of actual increases in cases. Increases in PCR testing are however consistent with national and increasingly global trends for PCR usage as the type of test to detect pertussis infections, particularly as a dominant test type in children under 15 years old.[16]

Vaccine type

Acellular pertussis vaccine has been in use for almost the entire period of observation for this study, 1997-2014. First introduced in Queensland in July 1997, acellular pertussis vaccine replaced the whole cell pertussis vaccine.[17] Over this time period, infants aged <6 months and particularly those aged <4 months have carried the highest burden of pertussis in Queensland - both in terms of notifications of pertussis and of death directly due to pertussis. For most of these young infants, pertussis occurs before they have had the opportunity to be protected by at least two doses of a

pertussis containing vaccine.[1] The United Kingdom recommended routine pertussis vaccination in pregnancy as a direct response to their high pertussis burden in early infancy and have shown that the program has been highly effective in reducing pertussis burden during early infancy.[18] In August 2014, Queensland introduced a funded pertussis vaccination program in pregnancy,[19] which became a national recommendation in Australia in 2015[1] and has now been funded by every state and territory across the country.[19]

Limitations

Missing data

Hospitalisation and vaccination data were not available within the dataset. Hospitalisation is an indicator of severity, whilst vaccination status is critical for assessment of vaccine failures.

Data for the variable 'Indigenous status' were missing in 70% of cases in the Queensland NOCS database from 1997-2014. Available data for 'Indigenous status' showed 10% of cases identified as being of Aboriginal and or Torres Strait Islander origin. This could be interpreted as an over representation of Aboriginal and Torres Strait Islander people in these data as the latest ABS figures estimates 3% of the total Australian population in 2013 identified as being Indigenous.[20] Care should therefore be taken when attempting to infer meaningful results from these data. Anecdotal reports by unpublished researchers suggest adding 'Indigenous status' to all laboratory request forms may improve under-identification in Aboriginal and Torres Strait Islander peoples.

In Queensland, deaths that occur directly as a result of a notifiable disease are not required to be formally notified and this is reflected in the data for the variable 'Died of condition'. Of the 53,901 individually notified cases, 97% of data were missing or unknown for this variable. Of the six deaths that were recorded, all were infants less than 6 months of age. It is difficult to make assumptions about these findings due to the lack of available data, however, other literature also support these results with most fatalities occurring in infants under 6 months of age.[5]

The results in this case series for notifications of pertussis by age are consistent with that of overseas literature. In these analyses, infants under 6 months of age recorded the highest notification rates of 196.5 per 100,000 populations. Rates declined sharply once infants reached over 12 months of age. This is consistent with an observational study of pertussis notifications by Carlsson et al.,[14] Their data collected on 1803 infants over a fifteen year period reported notification rates in those under 6 months of age to be 193 per 100,000 population with rates sharply declining once the infants were over 12 months old.

Conclusion

Although notification data are generally not used for analytical assumptions, they are an important indicator of how effective a surveillance system is operating or for quality assurance purposes. When the data are of high quality they provide important opportunities to observe trends and responses to interventions such as immunisation programs.

Whilst missing data provided some limitations for interpretability, the results in this case series for notifications of pertussis by age are consistent with that of overseas literature. As is the case globally, the increase in pertussis notifications has often coincided with a substantial increase in the number of cases being diagnosed by PCR method.

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Appendix 3.1   Stata do-file for Pertussis data analysis

```
*this do file was created by Lisa McHugh 02May2015 for MAE Pertussis data
analysis project
*Last updated 26Oct2015
*The do file labels, cleans and, where necessary, recodes the data with
outputs to various log files
capture log close
version 12.1
clear
set more off

* Change working directory in STATA, for me that's
cd "C:\MAE for uni\Pertussis data analysis\Data\
log using PertussisALL.log, replace

import excel "C:\MAE for uni\Pertussis data
analysis\Data\Pertussis\Pertussis_1997_2014_All _Stata.xlsx",
sheet("data_1997_2014") firstrow

*import excel "C:\MAE for uni\Pertussis data
analysis\Data\Pertussis_1997_2014_deidentified_Stata.xlsx", sheet("lab_data")
firstrow
*import excel "S:\QCMRI-RiOAR\FluMum Study National\MAE for uni\.xlsx",
sheet("data_1997_2014") firstrow

**DATA CLEANING**
*NOTES: THERE ARE NO HOSPITALISATION DATA
*Check for duplicates
duplicates report

foreach var of varlist AGE_AT_ONSET-ASSIGNED_PHU{
        codebook `var'
}
tab ASSIGNED_PHU

*Changing string variables to numerical
* GENDER
tab GENDER, miss
replace GENDER = "1" if GENDER == "F"
replace GENDER ="0" if GENDER =="M"
destring GENDER, replace
label define GENDERlbl 0 "Male" 1"Female"
label values GENDER GENDERlbl
tab GENDER

*INDIGENOUS STATUS
tab indig_status, miss
replace indig_status="1" if indig_status=="Indig"
replace indig_status="0" if indig_status=="Not Indigenous"
replace indig_status="." if indig_status=="Not Stated"
destring indig_status, replace
label define indig_statuslbl 0 "Not ATSI" 1 "Aboriginal & TSI"
label values indig_status indig_statuslbl
tab indig_status

*VALIDITY
tab VALIDITY, miss
replace VALIDITY="1" if VALIDITY=="VALID"
replace VALIDITY="0" if VALIDITY=="PROBABLE"
destring VALIDITY, replace
label define VALIDITYlbl 0 "Probable" 1 "Valid"
label values VALIDITY VALIDITYlbl
tab VALIDITY

*DATES-CHANGING FROM "MDY" TO "DMY"
foreach var of varlist Birthdate NOTIFICATION_DATE ONSETDATE DIAGNOSIS_DATE{
        codebook `var'
        format `var' %td
        codebook `var'
}
*DECEASED_DATE is a string variable & needs to be changed to numeric
```

```
codebook DECEASED_DATE
gen DeceasedDate=.
replace DeceasedDate=date(DECEASED_DATE,"DMY", 2015)
format DeceasedDate %d
label variable DeceasedDate "Deceased Date"
tab DeceasedDate

*GENERATE NOTIFICATION YEAR & MONTH
*create year and month of notification
gen Notifyear = year(NOTIFICATION_DATE)
label var Notifyear "Notification year"
drop if Notifyear==2015
gen Notifmonth = month(NOTIFICATION_DATE)
label var Notifmonth "Notification Month"
label define labelmonth 1 "Jan" 2 "Feb" 3 "Mar" 4 "Apr" 5 "May" 6 "Jun" 7
"Jul" 8 "Aug" 9 "Sep" 10 "Oct" 11 "Nov" 12 "Dec"
label values Notifmonth labelmonth
gen Notifyrmth = Notifyear + (Notifmonth*0.01)
label var Notifyrmth "Year month of notification"
tab Notifyear, miss
tab Notifmonth, miss
tab Notifyrmth, miss
hist Notifyear, discrete freq
tab indig_status Notifyear, miss
tab indig_status Notifyear, col

* AGE_AT_ONSET
tab AGE_AT_ONSET, miss
hist AGE_AT_ONSET,normal
summ AGE_AT_ONSET
*Create a variable to calculate age at time of onset of pertussis
gen Age=(ONSETDATE-Birthdate)/365.25
hist Age, normal
summ Age
br Age
*exclude cases where negative age numbers exist
drop if Age<0
br Age
*Age is not normally distributed so will need to use median instead of mean
summ Age, detail
*Look at median ages by notifcation year
tabstat Age, by (Notifyear) stat (n mean min p25 p50 p75 max)

*CREATE AGE GROUPS
egen Agegps=cut(Age), at (0,1,5,10,15,20,30,40,50,60,70,80,90,100)
label define Agegps ///
0 "0 years" ///
1 "1-4 years" ///
5 "5-9 years" ///
10 "10-14 years" ///
15 "15-19 years" ///
20 "20-29 years" ///
30 "30-39 years" ///
40 "40-49 years" ///
50 "50-59 years" ///
60 "60-69 years" ///
70 "70-79 years" ///
80 "80-89 years" ///
90 "90-99 years" ///
100 "100+ years"
tab Agegps

label var Agegps "Age groups"
tab Agegps indig_status
tab Agegps GENDER, col miss
tab Agegps Notifyear, col miss
hist Agegps
bysort GENDER: tab Notifyear Agegps
tab Notifyear Agegps, col miss
```

```
*Look at DISEASE BURDEN in WOMEN OF CHILD BEARING AGE (19-49 yrs?)
gen Childbearing=Age if Age>19 & Age <50 & GENDER==1
label var Childbearing "Childbearing"
sum Childbearing
gen men=GENDER if GENDER==0 & Age>19 & Age <50
label var men "Men 19-50yrs"
tab men, miss
gen women=GENDER if GENDER==1 & Age>19 & Age <50
label var women "Women childbearing age"
tab women


*Cases in 0-3 yr olds
gen Under3yr= Age if Age>0 & Age <=3.0
label var Under3yr "Children under 3yrs"
summ Under3yr
gen Agedays3yr = Age*365 if Under3yr<3
hist Under3yr


gen Agemonths3yr = Agedays3yr/30.5
label var Agemonths3yr "Child's age in months if under 3yrs"
format Agemonths3yr %12.1fc
tab Agemonths3yr


*Proportion of indig kids in this age group
tab indig_status if Under3yr<3


*Cases in 0-1 yr olds
gen Under1yr= Age if Age>0 & Age <=1.0
label var Under1yr "Children under 1yr"
summ Under1yr
hist Under1yr, normal
*To calculate number of days
gen Agedays1yr = Age*365 if Under1yr<1
summ Under1yr
summ Agedays1yr
*Proportion of indig kids in this age group
tab indig_status if Under1yr<1, miss
tab indig_status if Under1yr<1


graph box  Agedays1yr if Notifyear==1997
*Possibly do this for each year of notification then consolidte into the one
graph


*Cases in 0-6month old infants
gen Under6m= Age if Age>0 & Age <=0.6
label var Under6m "Infants under 6 months"
summ Under6m
hist Under6m, normal
* To calculate number of days
gen Agedays6m = Age*365 if Under6m
*Proportion of indig kids in this age group
tab indig_status if Under6m<=0.6, miss


*Infant Age Groups
gen InfantAge=3 if Under3yr<3
replace InfantAge=2 if InfantAge==3 & Agedays1yr<365.25
replace InfantAge=1 if InfantAge==2 & Agedays1yr<182.75
label define labelInfantAge 1 "<6mths" 2 "6mths-<1yr" 3 "1yr-3yrs"
label values InfantAge labelInfantAge
tab InfantAge
tab Notifyear InfantAge, col
tab GENDER InfantAge, col
tab indig_status InfantAge, col


*br VALIDITY Agegps Under3yr Under1yr Under6m
tab VALIDITY Agegps, col miss

*DAYS FROM ONSET OF ILLNESS TO NOTIFICATION DATE
gen Daysill=(NOTIFICATION_DATE-ONSETDATE)
*br Daysill NOTIFICATION_DATE ONSETDATE
```

```
*Some cases have illogic numbers of days (+ & -)
summ Daysill if Daysill>=0 & Daysill <215
tabstat Daysill, by (Agegps) stat (n mean min p25 p50 p75 max)
drop if Daysill<0
tabstat Daysill, by (Agegps) stat (n mean min p25 p50 p75 max)
drop if Daysill >215
tabstat Daysill, by (Agegps) stat (n mean min p25 p50 p75 max)
* These results may not be meaningful


*DIED OF CONDITION
tab Died_of_condition, miss
replace Died_of_condition = "1" if Died_of_condition == "Yes"
replace Died_of_condition ="0" if Died_of_condition =="No"
replace Died_of_condition =".u" if Died_of_condition =="Unknown"
destring Died_of_condition, replace
label define Died_of_conditionlbl 0 "No" 1"Yes"
label values Died_of_condition Died_of_conditionlbl
tab Died_of_condition Agegps, col miss
tab Died_of_condition Agegps
tab Died_of_condition InfantAge, col
*br Died_of_condition DeceasedDate Agegps Age indig_status Notifyear
Notifmonth Notifyrmth
*Note: ab(xx)is abbreviate to xx
bysort Died_of_condition: list Agegps Age indig_status Notifyear Notifmonth
Notifyrmth if Died_of_condition==1, ab(21)
sort NOTF_ref

save Pertussis_ALL.dta, replace
log close
```

```
*this do file was created by Lisa McHugh 12June2015 for MAE Pertussis LAB data
analysis project
*Last updated 26August2015
*The do file labels, cleans and, where necessary, recodes the data with
outputs to various log files
capture log close
version 12.1
clear
set more off
* Change working directory in STATA, for me that's
cd "C:\MAE for uni\Pertussis data analysis\Data\
log using PertussisLabAll.log, replace

*import excel "C:\MAE for uni\Pertussis data
analysis\Data\Pertussis_1997_2014_deidentified_Stata.xlsx",
sheet("data_1997_2014") firstrow
*import excel "S:\QCMRI-RiOAR\FluMum Study National\MAE for uni\.xlsx",
sheet("data_1997_2014") firstrow
import excel "C:\MAE for uni\Pertussis data
analysis\Data\Pertussis\Pertussis_1997_2014_All _Stata.xlsx",
sheet("Pertussis_lab_data") firstrow

**DATA CLEANING**
*NOTES: MMPL is a unit measurement micro moles per litre used for this
particular lab test

*Check for duplicates
duplicates report
*NOTF_ref is not unique here (multiple results for a single notification)
*bysort NOTF_ref: assert [_N]==1

*the following variables contain no data or are irrelevant so will be dropped
drop SIGN NUM_VALUE UNIT ORGANISM SEROGRP SEROTYPE SUBTYPE

tab RESULT
gen tagresult=1 if RESULT=="POSITIVE" | RESULT=="REACTIVE" | RESULT=="PCR
DETECTED" | RESULT== "BORDETELLA PERTUSSIS PCR DETECTED"
replace tagresult=2 if RESULT=="EQUIVOCAL" | RESULT=="BORDERLINE"
replace tagresult=3 if RESULT=="NEGATIVE"
replace tagresult=4 if RESULT==""
tab RESULT tagresult, miss

* sort NOTF_ref so that multiple entries of a given NOTF_ref show the positive
result first
sort NOTF_ref tagresult

*now create tags to show the lab records that are here more than once so you
can see 1 of 3, 2 of 3, 3 of 3 etc
bysort NOTF_ref: gen tagn=[_n]
bysort NOTF_ref: gen tagN=[_N]
br if tagN>1
*now drop missing RESULT if we have another lab record in the dataset for that
notification
list NOTF_ref TEST_TYPE RESULT tagresult tagn tagN if tagresult==4 & tagN>1,
noobs
drop if tagresult==4 & tagN>1

*repeat tagging of data now those records are dropped
drop tagn tagN
sort NOTF_ref tagresult
bysort NOTF_ref: gen tagn=[_n]
bysort NOTF_ref: gen tagN=[_N]

*now drop NEGATIVE RESULT if we have another lab record in the dataset for
that notification
drop if tagresult==3 & tagN>1

*repeat tagging of data now those records are dropped
drop tagn tagN
sort NOTF_ref tagresult
```

```
bysort NOTF_ref: gen tagn=[_n]
bysort NOTF_ref: gen tagN=[_N]

*now drop BORDERLINE/EQUIV RESULT if we have another lab record in the dataset
for that notification
drop if tagresult==2 & tagN>1

*repeat tagging of data now those records are dropped
drop tagn tagN
sort NOTF_ref tagresult
bysort NOTF_ref: gen tagn=[_n]
bysort NOTF_ref: gen tagN=[_N]

bysort RESULT:tab tagn tagN

*not sure whether to drop this one record or not, suggest keep until after
merge with notification data
*drop if RESULT=="NEGATIVE"

foreach var of varlist ONSET_DATE-RESULT{
        codebook `var'
}
*DATES-CHANGING FROM "MDY" TO "DMY"
foreach var of varlist ONSET_DATE{
        codebook `var'
        format `var' %td
        codebook `var'
}
*COLLECTDATE is a string variable & needs to be changed to numeric
gen CollectionDate=.
replace CollectionDate=date(COLLECTDATE,"DMY", 2015)
format CollectionDate %d
label variable CollectionDate "Collection Date"
codebook CollectionDate
br CollectionDate COLLECTDATE

*GENERATE ONSET YEAR & MONTH
*create year and month of onset of illness
gen Onsetyear = year(ONSET_DATE)
label var Onsetyear "Onset year"
gen Onsetmonth = month(ONSET_DATE)
label var Onsetmonth "Onset Month"
label define labelmonth 1 "Jan" 2 "Feb" 3 "Mar" 4 "Apr" 5 "May" 6 "Jun" 7
"Jul" 8 "Aug" 9 "Sep" 10 "Oct" 11 "Nov" 12 "Dec"
label values Onsetmonth labelmonth
gen Onsetyrmth = Onsetyear + (Onsetmonth*0.01)
label var Onsetyrmth "Year month of onset"
tab Onsetyear, miss
codebook Onsetmonth
codebook Onsetyrmth
hist Onsetyear, normal
hist Onsetyear, discrete frequency
hist Onsetmonth, discrete frequency

*GENERATE SPECIMEN COLLECTION YEAR & MONTH
*create year and month of collection dates of specimens
gen SpecimenCollection = year(CollectionDate)
label var SpecimenCollection "Year of specimen collection"
gen Specimenmonth = month(CollectionDate)
label var Specimenmonth "Month of specimen collection "
label define labelmonth1 1 "Jan" 2 "Feb" 3 "Mar" 4 "Apr" 5 "May" 6 "Jun" 7
"Jul" 8 "Aug" 9 "Sep" 10 "Oct" 11 "Nov" 12 "Dec"
label values Specimenmonth labelmonth1
gen Specimenyrmth = SpecimenCollection + (Specimenmonth*0.01)
label var Specimenyrmth "Year month of specimen collection"
tab SpecimenCollection, miss
codebook Specimenmonth
codebook Specimenyrmth
hist SpecimenCollection, normal
hist SpecimenCollection, discrete frequency
```

```
hist Specimenmonth, discrete frequency

*DAYS FROM ONSET OF ILLNESS TO SPECIMEN COLLECTION DATE
gen DaysillSpec=(CollectionDate-ONSET_DATE)
br DaysillSpec

*TYPE OF SPECIMEN
replace SPECIMEN = "1" if SPECIMEN == "Blood Sample"
replace SPECIMEN ="0" if SPECIMEN =="Nasopharyngeal aspirate" |
SPECIMEN=="Aspirate" | SPECIMEN=="Saliva"
replace SPECIMEN="2" if SPECIMEN =="Sputum"
replace SPECIMEN="3" if SPECIMEN =="Bronchial Washings" | SPECIMEN== "Lavage"
| SPECIMEN=="Tissue"
replace SPECIMEN="4" if SPECIMEN =="Swab"
replace SPECIMEN="5" if SPECIMEN =="Urine"
replace SPECIMEN="6" if SPECIMEN =="Faeces"
replace SPECIMEN="7" if SPECIMEN =="Other"
replace SPECIMEN="." if SPECIMEN ==""
destring SPECIMEN, replace
label define labelSPECIMEN 0 "NPA" 1"Blood sample" 2 "Sputum" 3 "Bronch
lavage" 4 "Swab-undefined" ///
5 "Urine" 6 "Faeces" 7 "Other"
label values SPECIMEN labelSPECIMEN
tab SPECIMEN, miss
tab SPECIMEN
*bysort SPECIMEN: tab Agegps once datasets are merged

*TYPE OF TEST
replace TEST_TYPE = "2" if TEST_TYPE == "Nucleic Acid Method"
replace TEST_TYPE ="3" if TEST_TYPE =="Serol IgA"
replace TEST_TYPE="4" if TEST_TYPE =="Serol IgG" | TEST_TYPE== "Serol IgM" |
TEST_TYPE=="Serol"
replace TEST_TYPE="1" if TEST_TYPE =="Isolation"
replace TEST_TYPE="5" if TEST_TYPE =="Antigen"
replace TEST_TYPE="." if TEST_TYPE =="."
destring TEST_TYPE, replace
label define labelTEST_TYPE 1 "Culture" 2"PCR" 3 "Serol IgA" 4 "Serol(IgA
unspecified)"  5 "Other"
label values TEST_TYPE labelTEST_TYPE
tab TEST_TYPE, miss
*bysort TEST_TYPE: tab Agegps once datasets are merged
tab TEST_TYPE tagN, miss

*now drop TEST_TYPE if test type is "Other" where there is another test result
for that case
list NOTF_ref TEST_TYPE RESULT tagn tagN if TEST_TYPE==5 & tagN>1, noobs
sort NOTF_ref
drop if TEST_TYPE ==5 & tagN>1
*repeat tagging of data now those records are dropped
drop tagn tagN
sort NOTF_ref TEST_TYPE
bysort NOTF_ref: gen tagn=[_n]
bysort NOTF_ref: gen tagN=[_N]
*now drop TEST_TYPE if test type is "Serology other than IgA" where there is
another test result for that case
br NOTF_ref TEST_TYPE RESULT tagn tagN if TEST_TYPE==4 & tagN>1
sort NOTF_ref
tab TEST_TYPE tagN, miss
drop if TEST_TYPE ==4 & tagN>1
tab TEST_TYPE tagN, miss
drop tagresult tagN tagn
*repeat tagging of data now those records are dropped
sort NOTF_ref TEST_TYPE
bysort NOTF_ref: gen tagn=[_n]
bysort NOTF_ref: gen tagN=[_N]
tab TEST_TYPE tagN, miss

*If duplicate results for the same test then keep the first record (sorted by
DaysillSpec)
```

```
list NOTF_ref ONSET_DATE COLLECTDATE DaysillSpec SPECIMEN TEST_TYPE RESULT
tagn tagN if DaysillSpec<0 & tagN>1 | NOTF_ref=="N01415", noobs
drop if DaysillSpec<0 & tagN>1

drop tagn tagN
*now search for exact duplicates of SPECIMEN, TEST_TYPE and RESULT
sort NOTF_ref SPECIMEN TEST_TYPE RESULT DaysillSpec
bysort NOTF_ref SPECIMEN TEST_TYPE RESULT: gen tagn=[_n]
bysort NOTF_ref SPECIMEN TEST_TYPE RESULT: gen tagN=[_N]
*br if tagN>1
*now dropping exact duplicates of SPECIMEN, TEST_TYPE and RESULT for the same
NOTF_ref
drop if tagN>1 & tagn>1
drop tagn tagN

*now recheck how many records there are with more than 1 lab result in the
database
sort NOTF_ref DaysillSpec
bysort NOTF_ref: gen tagn=[_n]
bysort NOTF_ref: gen tagN=[_N]
tab TEST_TYPE tagN, miss
tab TEST_TYPE tagN

drop tagN tagn
*keeping tagn to use as part of the reshape wide command in the
PertussisMaster.do file
*ask Ross about reshaping positive results into a single line per NOTF_ref
save PertussisLab_ALL.dta, replace
log close
```

```
*this do file was created by Lisa McHugh 12June2015 for MAE Pertussis
notifiations data analysis project
*Last updated 24Oct2015
*This master do file merges the Pertussis notification do file with the
Pertussis Lab data do file.
*It was painful to understand and work out and am glad it's over!

capture log close
version 12.1
clear
set more off
* Change working directory in STATA, for me that's
cd "C:\MAE for uni\Pertussis data analysis\Data\

*First run both do files right through to make sure there are no errors
do Pertussis_ALL
do PertussisLab_ALL
clear
log using PertussisMaster_ALL.log, replace
*reshape PertussisLab_ALL into a single unique record per line
use PertussisLab_ALL.dta
*confirm more than 1 lab result in PertussisLab.dta
sort NOTF_ref DaysillSpec
bysort NOTF_ref: gen tagn=[_n]

drop COLLECTDATE TEST_ID
* i is the index variable to sort the data by
reshape wide LAB_NAME SPECIMEN TEST_TYPE RESULT CollectionDate ///
SpecimenCollection Specimenmonth Specimenyrmth DaysillSpec, i(NOTF_ref)
j(tagn)

bysort NOTF_ref: assert [_N]==1
save PertussisLabmin.dta, replace
use Pertussis_ALL.dta
merge 1:1 NOTF_ref using PertussisLabmin.dta
tab _merge
*check merge results by notification year
tab Notifyear _merge

drop if Notifyear==2015

*br ONSETDATE Notifyear
bysort indig_status: tab Notifyear Agegps,miss
bysort Notifyear: tab GENDER Agegps, col

*GENERATING TYPES OF TESTS
gen PCRposTest=1 if (TEST_TYPE1==2 & RESULT1=="POSITIVE") | (TEST_TYPE2==2 &
RESULT2=="POSITIVE")| (TEST_TYPE3==2 & RESULT3=="POSITIVE")
label values PCRposTest labelPCRposTest
label var PCRposTest"PCR positive test"
*br PCRposTest TEST_TYPE1 RESULT1 TEST_TYPE2 RESULT2 TEST_TYPE3 RESULT3 if
PCRposTest==1
tab PCRposTest Notifyear if PCRposTest==1

gen CultureposTest=1 if (TEST_TYPE1==1 & RESULT1=="POSITIVE") | (TEST_TYPE2==1
& RESULT2=="POSITIVE") | (TEST_TYPE3==1 & RESULT3=="POSITIVE")
label values CultureposTest labelCultureposTest
label var CultureposTest"Culture positive test"
*br CultureposTest TEST_TYPE1 RESULT1 TEST_TYPE2 RESULT2 TEST_TYPE3 RESULT3 if
CultureposTest==1
tab CultureposTest Notifyear if CultureposTest==1

gen IgAposTest=1 if (TEST_TYPE1==3 & RESULT1=="POSITIVE")| (TEST_TYPE2==3 &
RESULT2=="POSITIVE") | (TEST_TYPE3==3 & RESULT3=="POSITIVE")
label values IgAposTest labelIgAposTest
label var IgAposTest"Serology IgA positive test"
*br IgAposTest TEST_TYPE1 RESULT1 TEST_TYPE2 RESULT2 TEST_TYPE3 RESULT3 if
IgAposTest==1
tab IgAposTest Notifyear if IgAposTest==1
```

```
gen SerologyposTest=1 if (TEST_TYPE1==4 & RESULT1=="POSITIVE")| (TEST_TYPE2==4
& RESULT2=="POSITIVE")| (TEST_TYPE3==4 & RESULT3=="POSITIVE")
label values SerologyposTest labelSerologyposTest
label var SerologyposTest"Serology unspecified positive test"
*br SerologyposTest TEST_TYPE1 RESULT1 TEST_TYPE2 RESULT2 TEST_TYPE3 RESULT3
if SerologyposTest==1
tab SerologyposTest Notifyear if SerologyposTest==1

gen OtherposTest=1 if (TEST_TYPE1==5 & RESULT1=="POSITIVE") | (TEST_TYPE2==5 &
RESULT2=="POSITIVE") | (TEST_TYPE3==5 & RESULT3=="POSITIVE")
label values OtherposTest labelOtherposTest
label var OtherposTest"Other positive test"
*br OtherposTest TEST_TYPE1 RESULT1 TEST_TYPE2 RESULT2 TEST_TYPE3 RESULT3 if
OtherposTest==1
tab OtherposTest Notifyear if OtherposTest==1

tabstat PCRposTest CultureposTest IgAposTest SerologyposTest OtherposTest, by
(Notifyear)  stat (n)

*Look at type of test by age groups.
*NB: no data before 2000
tab Agegps TEST_TYPE1 if Notifyear>2000
tab Agegps TEST_TYPE1 if Notifyear>2007
tab Agegps TEST_TYPE1 if Notifyear>2000 & Notifyear<2008

save PertussisMasterALL.dta, replace
log close
```

4. Outbreak Investigation of Salmonella Typhimurium following consumption of Korean style sushi in Brisbane January 2015

Dozens sickened: Sushi source of another Salmonella outbreak in Brisbane

Fresh off the Salmonella-in-deep-fried-ice-cream outbreak which sickened at least 130 people in Brisbane, health types fear there could be more victims of food poisoning after dozens of people became sick from eating sushi sold in Asian grocery stores in Brisbane.

http://bcove.me/hvprnsiy

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Prologue

Background

Kim Bap sushi is a form of sushi also known as 'Gimbap' or 'kimbap'; it will be referred to as Kim Bap throughout the remainder of this chapter. Kim Bap is similar to the Japanese variety of sushi however it originates from Korea. Kim Bap is literally 'seaweed rice', the two main ingredients of the dish; it is often served with multiple variations of fillings and pickled radish. Unlike traditional Japanese sushi that uses rice vinegar to season the rice, Korean sushi uses sesame oil and salt.[1] The common fillings used in Kim Bap sushi are fish cakes, imitation crab meat, ham, eggs, seasoned beef, cucumbers, carrots and spinach.[1]

My role

My placement was based at the Communicable Diseases Branch of Queensland Health. There were many foodborne outbreak investigations occurring in Brisbane at the particular time of my placement. Under the guidance of the Acting Director of the Metropolitan South public health unit and one of the senior epidemiologists I led a high profile outbreak investigation assessing causes of *Salmonella* Typhimurium. I was involved in the response from the outset of this investigation and my tasks included interviewing cases, creating a line list, management of laboratory specimen results, data entry, data analysis, interpretation of the data and report writing.

Lessons Learned

This outbreak investigation was a valuable learning opportunity in many ways. It was my first experience working inside a public health unit and the warm welcome I received was encouraging and appreciated. I gained skills in transforming concepts learned in courseblock into practice, and quickly became aware of the reality of the speed of the response to a public health crisis, which was not a sequential ten step plan but involved implementing all steps at the same time!

Observing how community concerns were responded to throughout the outbreak investigation and the way media attention was managed by professional and respectful communication within the public health unit was insightful and refreshing.

During the outbreak all staff co-ordinated efforts during a particularly frantic period where multiple outbreaks within the public health unit were being managed.

Public Health Implications

This outbreak affected over 100 members of the Korean community in greater Brisbane and the degree of illness experienced was severe. There were twenty-two hospitalisations of adults and children, and a perinatal event causing a premature birth. These factors precipitated wide spread media interest in the outbreak coverage.

Efforts to control this outbreak were successful in that prompt and effective actions were taken to stop further members of the community from falling ill. This included the implementation of an effective communication strategy developed and implemented by the Metropolitan South public health unit to deal with the media and those concerned in the wider Brisbane community. As a result of the outbreak, awareness of food safety measures was raised within the Korean community and food retailers. Food retailers were provided with advice regarding food safety matters and it was recommended that they ensure ongoing compliance with the *Food Safety Standards* and the *Food Act 2006.*

Acknowledgements

Abstract

Introduction

On Thursday 15 January 2015 the Metropolitan South Public Health Unit in South Brisbane received notification that multiple people had presented with signs and symptoms of a gastrointestinal illness to health care facilities. All patients had experienced symptoms consistent with gastroenteritis following consumption of Kim Bap sushi purchased from multiple food outlets in Brisbane. The dates of onset of illness initially occurred over a three-day period from 13 to 16, January 2015.Laboratory analysis of faecal samples confirmed Salmonella Typhimurium was the organism with MLVA patterns consistent for all cases.

Methods

This outbreak investigation was a descriptive study involving epidemiological, laboratory and environmental investigations. Information was collected using a working case definition and hypothesis generating interviews. Data analysis included calculating medians, frequencies and proportions of implicated food exposures. All food samples and environmental swabs were tested using culture for Salmonellae species and other bacterial organisms at the QHFSS laboratory at Coopers Plains

Results

There were 85 confirmed cases of Salmonella Typhimurium who completed a questionnaire and provided faecal samples. Most were female, 51 (60%) and 34 were male. The median age of cases was 31 years (range <1 – 66 years).Twenty-two cases were hospitalised, 7 of these (32%) were children. All cases reported a history of diarrhoea. Laboratory analyses identified as the agent of infection.

Conclusions

There was enough evidence to indicate the aetiological agents responsible for illness in this outbreak were *Salmonella* Typhimurium MLVA 03-12-11-12-524 and MLVA 03-13-11-12-524. The likely vehicle of transmission of infection for this outbreak was Kim Bap sushi which was distributed by one producer to multiple food retail outlets in Brisbane. Supply of this product ceased on Friday 16 January, 2015 and there were no further reported cases of illness. I was unable to determine any associations between food exposures and illness due to the absence of a comparison group.

Introduction

Salmonella are Gram-negative bacteria ubiquitous in the environment.[2] Infection in humans is usually brought about by consumption of contaminated food via the faecal-oral route. Multiple potential food sources, generally of animal origin, have been implicated.[2] Most *Salmonella* arise from a single species, *Salmonella enterica*, sub species enterica, from which there have been over 2,500 serotypes identified to date.[2] Over 99% of all Salmonellae infections in *humans* are caused by this species.[2] *Salmonella* Typhimurium are a serovar of the sub species *enterica* and are considered highly prevalent globally and within Australia.[2] The five year mean annual case notification rate of Salmonellosis in Australia (2007-2011) was 46.6 per 100,000 population per year, with the *Salmonella* Typhimurium serotype accounting for approximately 40% of notifications in Victoria and Queensland.[3] Human infection with *Salmonella* Typhimurium has been linked with multiple animal hosts and in Western Australia in particular is linked to certain flocks of chicken and chicken meat.[4]

The incubation period for *Salmonella* is 6 to 72 hours.[2] Those infected typically present with a sudden onset of gastrointestinal symptoms such as nausea and vomiting, diarrhoea, fever and abdominal pain with symptoms sometimes persisting for weeks.[2] Outbreaks of Salmonellosis are common, although 60-80% of known cases are considered to occur sporadically.[2]

Salmonella infections are notifiable in all jurisdictions in Australia.[5]Only confirmed cases are notifiable. Confirmation requires definitive laboratory evidence of isolation or detection of *Salmonellae* species excluding *Salmonella* typhi which is a separate notification.[5] Confirmation of diagnosis in Queensland is predominantly attained through the testing of faecal specimens using a range of laboratory-based techniques such as culture or nucleic acid amplification tests (NAAT's), for example polymerase chain reaction (PCR) testing. Isolates are then sent for serotyping, phage-typing or Multiple Locus Variable-number tandem repeat Analysis (MLVA) to further characterise the pathogen. Rates of *Salmonella* notifications have risen steadily in Queensland over time, particularly from December 2014 [6] when over 55% of cases were serotyped as *Salmonella* Typhimurium. *Salmonella* Typhimurium was the serovar identified in the outbreak presented in this chapter.

Identification of an outbreak

On Thursday 15 January 2015 the Metropolitan South Public Health Unit (MSPHU) in South-East Brisbane received notification of five people who had presented with gastrointestinal symptoms to an astute General Practitioner (GP) at Eight Mile Plains. A further four people had presented to the Queen Elizabeth II Hospital emergency department (also located in South Brisbane), with signs and symptoms of a gastrointestinal illness. The GP and the clinician treating the hospitalised people notified the public health unit. A food-borne illness outbreak was hypothesised after reports confirmed that all patients had experienced symptoms of abdominal cramps, diarrhoea and vomiting following consumption of Kim Bap sushi purchased from multiple food outlets in Brisbane. The dates of onset of illness initially occurred over a three-day period from 13 to 16, January 2015.

On 15 January, 2015 an outbreak control team (OCT) meeting was initiated at MSPHU and outbreak investigation team members were identified. The outbreak investigation was led by the Acting Director of the public health unit (PHU) and the team included a Public Health Physician, epidemiologists, laboratory scientists, environmental health officers (EHO), public health nurses, an OzFoodNet epidemiologist and myself. Early in the outbreak, after reviewing verbal and written reports from the GP and other clinicians attending to the cases, we ascertained that all people with illness had eaten Korean sushi (Kim Bap) from a number of Asian retailers, Korean grocers and Asian supermarkets. Concurrently a statement from the Queensland Health Forensics and Scientific Services (QHFSS) laboratory confirmed the MLVA patterns from faecal specimens were consistent with all cases.

The purpose of the outbreak investigation was to determine the source of *Salmonella* Typhimurium infection and instigate control measures to prevent further illness from occurring in the community. The focus was also on identifying factors contributing to contamination, growth or survival of the responsible pathogen. There were also concerns from medical practitioners attending to the cases and from scientists at the QHFSS regarding the virulence of this particular strain due to the severity of symptoms. A communication strategy was devised and initiated by the Acting Director of the MSPHU to deal with interest from the media and those concerned about the outbreak

in the wider Brisbane community. This strategy included providing daily updates to the media on the progress of the outbreak investigation. This chapter describes the ensuing outbreak and the public health response to the investigation.

Methods

Epidemiological investigation

After reviewing the initial data, the outbreak investigation team developed a working hypothesis that the consumption of a variety of Kim Bap Korean style sushi was responsible for illness. This sushi was being sold by multiple Asian grocers across the south Brisbane metropolitan area.

Case definition

A case was defined as any person who consumed Korean style Kim Bap sushi from 13 to 21 January 2015 and who subsequently developed diarrhoea and/or vomiting and/or stomach cramps within 72 hours of consuming the sushi. The case definition date of 13 January 2015 was chosen based on discussions with retailers who stocked Kim Bap sushi. These discussions revealed the product had not been delivered over the Christmas and New Year period and deliveries resumed 13 January 2015.

Study design

The study design for this outbreak investigation was a descriptive study. A decision was made by the Acting Director of the facilitating public health unit early in the outbreak not to conduct an analytic study due to the numerous other outbreaks that were occurring in the public health unit at the time.

Data collection

A line list was developed in a Microsoft Excel spreadsheet. The line list was based on incoming notification data from the Queensland Health Forensic Scientific Services (QHFSS) laboratory and clinicians. People who met the case definition were interviewed by trained public health staff. I was also involved with interviewing cases. Cases were interviewed using the Queensland Health suspected food borne illness

outbreak hypothesis generating questionnaire. A three-day food diary was used as a prompt in the hypothesis generating interview process. The study variables included in the dataset are shown in the box below, including a list of food items consumed by the cases, which were gathered from the interview process and then categorised.

Outbreak identification #	Outbreak venue	Food items consumed
Notification date	Attendance date	• Rice
Diagnosis date	Nausea	• Egg
Interview date	Vomiting	• Tuna
Date of onset of illness	Diarrhoea	• Carrot
Date of birth	Abdominal cramps	• Pickled radish
Age at onset of illness	Blood in stools	• Cucumber
Sex	Fever	• lettuce
Suburb	Duration of illness (in days)	• Ham
Postcode	Hospitalisation	• Seafood extender
Public health unit	Days hospitalised	• Crab
Epi linked case		• Sesame seeds
		• Seaweed
		• Sesame oil

Analysis

Data were analysed using Stata version 12.1 (StataCorp, Texas, USA) to conduct descriptive analyses. I calculated frequencies and proportions of implicated food exposures and calculated medians for continuous variables. In Stata, dates were formatted and remaining variables were coded as either categorical or binary. Age groups were created. I was unable to determine any associations between food exposures and illness due to the absence of a comparison group.

Laboratory investigation

Faecal specimens were collected from cases requesting isolation or detection of *Salmonellae* species. All faecal samples were sent directly to QHFSS or indirectly to QHFSS from private pathology providers. Samples that were positive for *Salmonella* by culture were typed by PCR method and subsequently MLVA tested and genotyped. The QHFSS laboratory variables included in the analysis are shown in the adjacent box.

> Outbreak identification number
> Notification date
> Diagnosis date
> Date of onset of illness
> Date of birth
> Public health unit
> Laboratory number
> Specimen type
> Collection date of specimen

Environmental investigation

The environmental health investigation included joint inspections by MSPHU and Brisbane City Council (BCC) to a number of retail food outlets. This involved food sampling and multiple environmental swabbing of surfaces such as kitchens and benches by environmental health officers (EHO) from the retail food outlets. A joint inspection of the residential home of the Kim Bap sushi operator was conducted by BCC, MSPHU and Queensland Police Service (QPS) officers as it was suspected that sushi was being prepared in the kitchen of his private residential house. Food samples and environmental swabs were also obtained from these premises and student flatmates living at the premises were interviewed.

All food samples and environmental swabs were tested using culture for Salmonellae species and other bacterial organisms at the QHFSS laboratory at Coopers Plains, Brisbane.

Results

Epidemiological investigation

There were 100 cases identified in this outbreak with onset dates from 13 to 21 January 2015. All cases ate some type of Kim Bap sushi.

Person

There were 100 known people who consumed Kim Bap sushi between 13 and 16 January 2015 and developed gastrointestinal symptoms. A total of 96 (96%) were of Korean ethnicity with English as a second language. Of these 100 people with known gastrointestinal symptoms, 85 (85%) were interviewed and 58/85 (68%) provided faecal specimens to QHFSS for analysis. Of the 58 faecal specimens provided and tested, 100% were positive for either *Salmonella* Typhimurium MLVA 03-12-11-12-524 (91%) or MLVA 03-13-11-12-524 (9%). A further 27 faecal specimens provided by the cases had been sent to and tested by other laboratories. Confirmation from these laboratories that the faecal samples were positive for *Salmonella* Typhimurium was provided. Initially it was difficult to contact people for further information due to the severity of their illness and language difficulties. There were a remaining 15/ 100 (15%) who refused to be interviewed or refused to provide a specimen or were unable to be recontacted.

Of the 85 people who completed a questionnaire, 51 were female (60%) and 34 were male. The median age of cases was 31 years (range <1 – 66 years).
The majority of cases (37%) occurred in the 30-39 year old age group (Figure 4.1).

Figure 4.1: Age group of 85 patients with *Salmonella* Typhimurium, South Brisbane, January 2015
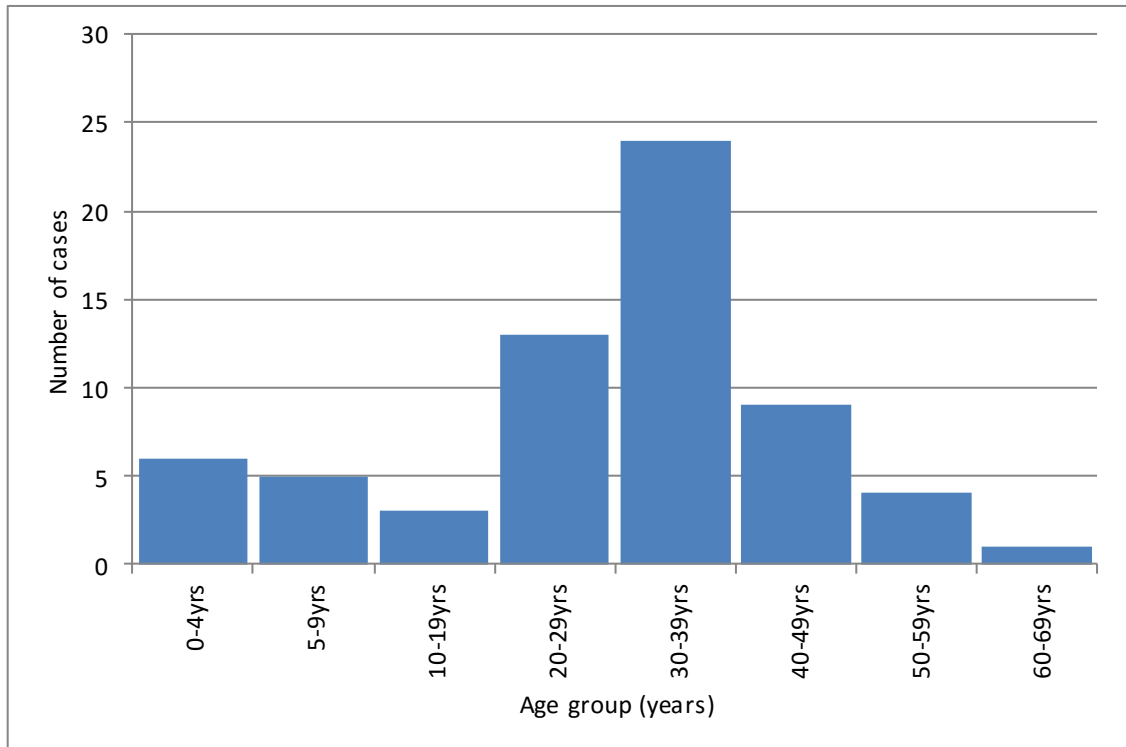
Twenty-two cases were hospitalised, seven of these (32%) were children. Two cases were pregnant women, one of whom delivered prematurely at 31 weeks gestation once gastroenteritis symptoms began and one who was 38 weeks gestation and birthed her infant immediately upon becoming ill.

Time

Six cases reported that the date of onset of their illness commenced on 13 January 2015. There were 44 cases who reported illness commencing on the 14 January 2015 with the last known recorded cases reporting illness commencing on the 20 January, (Figure 4.2).

Figure 4.2: **Confirmed cases of *Salmonella* Typhimurium by date of onset of illness, South Brisbane, January 2015**
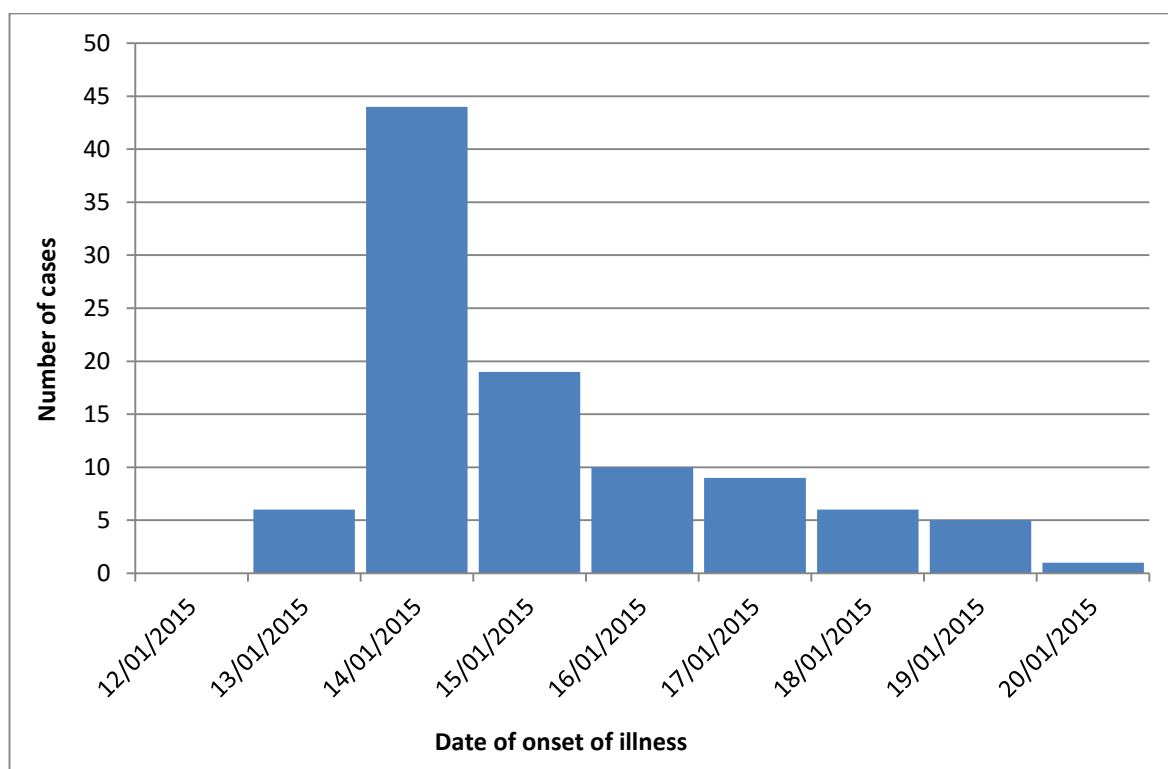
The median incubation period for this outbreak was 17 hours (range 6 to 51 hours). The median duration of illness was difficult to determine due to ongoing illness; at the time of interview all but two cases were still experiencing symptoms. The duration of illness for these two cases was 6 and 10 days.

Place

All cases purchased Kim Bap sushi products from a total of 22 Korean food retailers throughout Brisbane in January 2015. Cooked rice and sesame oil was contained in all of the pre-packaged sushi. Apart from the rice and sesame oil (where 100% of cases consumed these food items), egg was the next most commonly consumed food item (45; 69%), followed by tuna (42; 65%) and a variety of vegetables (41; 63%)(Table 4.1).

Table 4.1:   **Kim Bap sushi food items consumed by 70 cases with *Salmonellosis*, South Brisbane 2015**

Food item consumed	N (%)
Rice	70/70 (100%)
Egg	45/65 (69%)
Tuna	42/70 (65%)
Vegetables including carrot, pickled radish, cucumber, lettuce	41/70 (63%)
Ham	34/70 (52%)
Seafood extender	7/70 (10%)

NOTE: denominators differ due to missing data

Clinical features

All cases (100%) reported a history of diarrhoea and 57/62 (92%) reported stomach cramps. The remaining symptoms reported by cases are listed in Table 4.2. Laboratory scientists from QHFSS indicated this strain of *Salmonella* Typhimurium appeared to be particularly virulent (personal communication: QHFSS, January 2015).

Table 4.2:   **Symptoms of 65 people with *Salmonellosis* who consumed Kim Bap sushi, Brisbane, 2015**

Symptoms	N (%)
Diarrhoea	65/65 (100%)
Stomach cramps	57/62 (92%)
Fever	56/64 (88%)
Headache	52/61 (85%)
Nausea	39/58 (67%)
Vomiting	33/64 (52%)
Blood in stools	1/52 (2%)

NOTE: denominators differ due to missing data

Laboratory investigation

A total of 58 cases provided faecal specimens. All returned positive results for *Salmonella* Typhimurium and were further characterised to have MLVA patterns 03-12-11-12-524 or 03-13-11-12-524. Fifty three specimens (91%) were MLVA pattern 03-12-11-12-524 and five (9%) were MLVA pattern 03-13-11-12-524.

Leftover food samples of Kim Bap sushi collected from one retail food outlet were positive for *Salmonella* Typhimurium MLVA 03-12-11-12-524 (Figure 4.3)**.** Pre-prepared Korean sushi was not found at the owner/operator's residential premises at the time of the inspection. Commercial quantities of food were found however, that would normally be used to prepare Kim Bap sushi. These food samples obtained from the owner/operator's residential premises did not contain any positive results for *Salmonella.* An unknown quantity of environmental swabs detected *Bacillus cereus.*

Figure 4.3: **Sample of pre-packaged Kim Bap sushi implicated in the *Salmonella* Typhimurium outbreak, South Brisbane, 2015**

Source: http://www.ninemsm.com/en-au/video/watch/sushi-salmonella-scandal
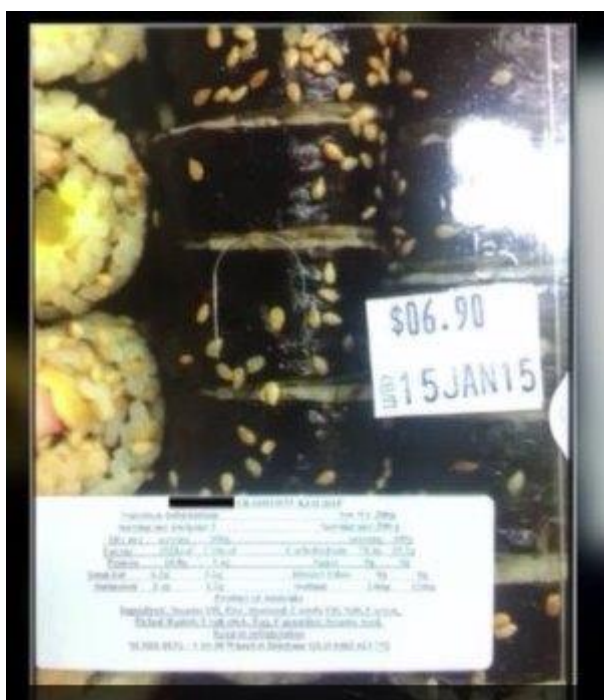
Environmental Health Investigation

Results from the environmental health inspections led to the suspension of the licence of one premise due to the identification of poor food hygiene practices. Another premise did not have a food licence from BCC. Another one Asian grocer surrendered their food licence following an interview. The environmental health investigation identified that ten staff members from another premise experienced symptoms of gastroenteritis during the outbreak. However, none of them sought medical treatment and they all stated that they did not wish to be interviewed or supply a faecal sample.

Upon interview, student flatmates of the owner denied that any food preparation took place at the owner's residence. Flatmates would not reveal where food was prepared nor the whereabouts of the owner. The owner/operator who manufactured the Kim Bap sushi was unable to be located, despite repeated attempts to contact him.

The owner/operator was a Korean student living in Brisbane who held a student visa. He worked in a local food retail company who supplied produce to the Korean food retailers in Brisbane. These were the same retailers that he was supplying Kim Bap sushi to. A Korean community spokesperson indicated that many individuals were keen to find and speak with the owner/operator as they were angry and were contemplating legal action. It was alleged that the owner/operator had left Australia. The MSPHU attempted to confirm this information with the Department of Immigration and Border Protection but were unsuccessful. The owner/operator was unable to be located, therefore he was unable to be issued with notices and MSPHU were unable to obtain any further information to instigate a traceback of food suppliers. There were no further reported cases of *Salmonella* Typhimurium from consumption of Kim Bap sushi in the Brisbane city following the environmental investigation.

Discussion

A Queensland OzFoodNet Enteric Disease Surveillance Report for the 24 January 2015 recorded 7 outbreaks of *Salmonella* Typhimurium infection that required investigation in South East Queensland from mid-December 2014 (personal communication: Russell Stafford, QH 2015). According to this report, *Salmonella* notifications were 2.2 times higher than the preceding 5-year mean for this time period, with 55% of cases serotyped as *Salmonella* Typhimurium. It is thought possible that the use of PCR to diagnose *Salmonella* Typhimurium has had a role in diagnoses over time.[10] Testing faeces using PCR commenced in private laboratories and public laboratories in the last five years (2009-2014). [11]

The time period when the outbreak occurred was considered a particularly hot summer with higher than average daily temperatures for a longer numbers of days (personal communication: John Bates QHFSS, January 2015). Records for mean maximum daily temperatures in Queensland from the Australian Bureau of Meteorology, [7]showed November 2014 was the hottest month since before 1999 when online data became available.[9] December 2014 also recorded the highest mean maximum temperature in 3 years.[9] In January 2015 when the outbreak occurred, mean maximum temperatures were highest for the third consecutive year in a row.[9] Other *Salmonella* outbreak reports in Australia that have noted highly virulent serovar strains have also occurred during or following particularly hot summers.[3] Recent literature from Adelaide also demonstrated that there are more notifications of *Salmonella* Typhimurium when higher temperatures are recorded. [10]

The MLVA pattern for 6 out of 7 of the outbreaks that occurred in Brisbane mentioned above was *Salmonella* Typhimurium MLVA 03-12-11-12-524 which was the same MLVA pattern noted in this outbreak. Scientists from the QHFSS stated this particular serovar was showing high virulence and as a result, this factor combined with the actual outbreak itself caused intense media scrutiny, requiring the Acting Director of MSPHU to provide regular updates regarding the progress of the investigation.

The same Queensland Health suspected food borne illness outbreak questionnaire was used by trained public health personnel for each case when conducting the interviews. This will contribute to minimising any potential measurement bias. This is also true for the validity of laboratory results for the faecal samples tested.

Final results from the epidemiological investigation for this outbreak were written and presented in a report to the MSPHU. The report described the management and analyses of data obtained through interviews; the report also contained the results from the laboratory and environmental investigations.

Kim Bap sushi is sold pre-made and pre-packaged.[1] The sushi contains multiple high-risk food items known to contribute to Salmonellosis.[2] Cross contamination is a strong possibility and could have occurred during the preparation process. That combined with the fact that each sushi roll contains multiple ingredients meant that it was not possible to determine the primary source of the contaminated food.

Limitations

Conducting the interviews for the cases proved difficult due to the severity of their illness and English as a second language for the majority of Korean speaking participants. Interpreters were not used during the interview process due to the limited available financial resources and the time constraints incurred due to other outbreaks in the PHU at the time. It is therefore possible that some misinterpretation may have occurred during the interview process. Despite these difficulties, recall error for the cases is unlikely due to the severity of their symptoms, the pre-packaged and clearly labelled sushi containers, and the minimal time frame from the onset and notification of illness to being interviewed by public health staff. The intense media coverage (Figure 4.4) may have prompted more people with symptoms of gastroenteritis to seek medical attention and this may have potentially identified more cases.

Figure 4.4: **Media coverage of *Salmonella* outbreak related to consumption of Kim Bap sushi, South Brisbane, 2015**

Source: http://www.ninemsm.com/en-au/video/watch/sushi-salmonella-scandal

Whilst an analytical study such as a case-control study would have been the preferred method of study design for this outbreak, it was not practical, nor cost-effective to do so, given other competing health priorities. It was clear from early on in this outbreak that consumption of Korean sushi was generating the illness experienced by cases, however there were limited samples of the remaining product to conduct any further testing.

Conclusion

On balance there was enough evidence to indicate the aetiological agents responsible for illness in this outbreak were *Salmonella* Typhimurium MLVA 03-12-11-12-524 and MLVA 03-13-11-12-524. The likely vehicle of transmission of infection for this outbreak was Kim Bap sushi which was distributed by one producer to multiple food retail outlets in Brisbane. Supply of this product ceased on Friday 16 January, 2015 and there were no further reported cases of illness.

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5.   Evaluation of the Queensland Notifiable Conditions System for surveillance of hepatitis A virus

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Prologue

A core component of the MAE field program is to evaluate a local surveillance system. I evaluated the Notifiable and Other Conditions System for hepatitis A notifications in Queensland. This chapter follows the structure of the framework used by Teutsch and Churchill (2000) and the Centers for Disease Control updated guidelines for evaluating a public health surveillance system (2001). As such, this chapter does not contain a traditional discussion section; instead I have opted to include the discussion within the results section. I have done so to enhance the readability of the evaluation, which included a substantive case series analysis of hepatitis A notifications in Queensland 1988-2014. I was invited to give an oral presentation of preliminary results of the data analysis component of this project at the Communicable Disease Control conference in Brisbane June 2015 (Appendix 5.1).

My role

I completed a detailed data analysis of all hepatitis A notifications in Queensland for the period 1988-2014. I designed questionnaires for the purpose of conducting stakeholder interviews of current users of the surveillance system. I appraised the responses to gain insights into the way the current surveillance system was performing. I examined five surveillance system attributes and developed recommendations to improve the functioning of the system. I also played a role in the multi state hepatitis A outbreak related to frozen berries, March 2015. This involved conducting case control interviews and data entry into NetEpi.

Lessons Learned

This project was a huge learning opportunity regarding the many elements involved in conducting an evaluation of a public health surveillance system. I found it a complex process bringing all these components of the project together into one final report. I also learned that you cannot die from giving an oral presentation despite feeling like this is quite possibly going to happen.

Public Health Impact

Adequately functioning public health surveillance systems are essential in order to recognise outbreaks and changes in trends of infectious diseases. For the current hepatitis A

surveillance system to perform at its desired level, regular ongoing evaluations of the data and systems are necessary. As with all systems, some aspects function at a higher level than others and it is a matter of trying to get the balance right. Hopefully the limitations identified from this evaluation will be useful. The timely identification and control of hepatitis A infections is critical in reducing the transmission of this preventable disease and is a strength of the current surveillance system in Queensland.

Acknowledgements

Abstract

Introduction

Hepatitis A virus (HAV) in Australia remains a nationally notifiable disease and control is considered to be a high public health priority. Hospitalisations for HAV amongst Aboriginal and Torres Strait Islander children had been more than 100 times more common than amongst other children. The evidence now suggests that the gap has been closed, and indeed reversed in regards to hospitalisations and notifications. Queensland has played a pivotal role in this success.

Methods

This evaluation was conducted using the framework by Teutsch and Churchill (2000) and the Centers for Disease Control updated guidelines for evaluating public health surveillance systems. Short open ended Stakeholder questionnaires were employed to determine acceptability and timeliness of the system. A retrospective case series and genotype analysis was conducted to determine sensitivity, representativeness and data quality of the current system.

Results

There were 6748 single laboratory notified HAV cases extracted from the NOCS database for the period 1 January 1988 to 1 May 2014. OzFoodNet enhanced surveillance data for 192 laboratory confirmed notified cases of HAV from 2006-2014 were included in the analyses. Age and sex data were 99% complete. The median age of cases was 25 years (range: less than one year to 97 years), 58% of all notifications were male. The age-sex profile was typical of what would be expected in a setting where endemic HAV transmission has been interrupted, suggesting that the notification data are representative of the HAV cases in Queensland for this time period. Risk factor data were largely incomplete. Data quality for travel history, post exposure prophylaxis vaccination, Indigenous status, mechanism of infection and hospitalisations were poor.

Conclusions

There has been a change in the landscape over time for HAV notifications in Queensland. Most cases are now acquired as a result of overseas travel or exposure to a returning overseas traveller. Improved vaccination rates in prospective overseas travellers in all areas

of health care provider service could reduce current case numbers even further. Regarding the current HAV surveillance system's functionality; the timeliness of all aspects of the current system is reassuring as notifications are managed and processed within appropriate time frames. There needs to be a sustained improvement in completeness of data at every step for identification of Aboriginal and Torres Strait Islander people and for risk factor data.

Introduction

Hepatitis A (HAV) is a picornavirus.[1] The virus is considered an enteric pathogen, primarily transmitted person to person by the faecal-oral route, with infection affecting the liver.[1] Hepatitis A infections can be asymptomatic. Mild symptoms of infection with HAV such as fever, malaise, nausea, anorexia and abdominal pain are predominantly reported more in children whereas significant morbidity is reported more frequently among adults.[2] Jaundice, dark urine and pale coloured stools may also occur with any degree of severity.[1] Hepatitis A has a long incubation period from 15 - 50 days though most commonly 28-30 days. Treatment is based upon clinical findings.[1] The case-fatality rate for HAV is considered to be low at 0.1%-0.3% although slightly higher (1.8%) in adults over the age of 50 years.[1]

The diagnosis and control of HAV is a world-wide public health priority. In 2010 the global burden of disease related to deaths from acute HAV for both sexes of all ages was estimated to be 102,850 people and 4,351,760 disability-adjusted life years.[2] In 2014, the World Health Organization (WHO) estimated that there were 1.4 million people infected with HAV every year worldwide.[3] Exposure to a common source of contaminated food or water or exposure to sewerage are important environmental health factors related to HAV transmission in developing countries.[1] Globally, endemicity of HAV is separated into three levels; high, intermediate and low, with each level being directly related to sanitation and hygiene conditions.[3] Australia is currently (2015) considered to be in a low endemicity period. [3]

In Australia, hospitalisations for hepatitis A amongst Aboriginal and Torres Strait Islander children had been more than 100 times more common than amongst other children, but the evidence now suggests that the gap has been closed, and indeed reversed in regards to hospitalisations and notifications.[4] Queensland has played a pivotal role in this success. In June 1988, HAV became notifiable in Queensland in accordance with State legislation.[5] In 1999, a hepatitis A vaccine program was introduced for Aboriginal and Torres Strait Islander children under two years of age in North Queensland (hepatitis A vaccine was introduced into Australia in 1993).[6] Hanna *et al.*[7] showed the roll-out of this vaccination program significantly reduced HAV notification rates in the target population group. In 2005, this prompted an extension of the vaccination program to include Aboriginal and/or Torres

Strait Islander children less than two years of age in other Australian States and the Northern Territory. Hepatitis A virus in Australia remains a nationally notifiable disease and control is considered to be a high public health priority.[8]

The public health concern around HAV in Australia is particularly directed toward those at greater risk of acquiring the virus.[3] At-risk groups, (listed in Table 5.1) are a priority target group for HAV vaccination. The recommended doses and schedules for the hepatitis A vaccine are included in the 2013 Australian Immunisation Handbook.[6]

Table 5.1:   **Known risk groups for acquisition of hepatitis A virus, in the Australian context**

Travellers to an area where hepatitis A is highly endemic, particularly without prior vaccination

Aboriginal and Torres Strait Islander peoples

People who live in areas of poor sanitation and unsafe drinking water

Intravenous drug users

Men who have sex with men

Immunocompromised peoples

Persons who live or come into close contact with an infected person

Child care workers, aged care workers or others who reside or work in institutional facilities

Evaluation Objectives

In this chapter I describe an evaluation of the performance of the current HAV surveillance system in Queensland. The objectives of this evaluation were to:

- Describe the current epidemiology of HAV in Queensland and its public health importance;

- Analyse genotype data to determine whether there was a circulating endemic HAV strain in Queensland;

- Outline how the existing surveillance system supports the requirements for reporting and managing cases of HAV in Queensland;

- Assess the surveillance system attributes based on the Centers for Disease Control (CDC) *updated guidelines for evaluating public health surveillance systems*;[9]

- Present recommendations to improve the current HAV surveillance system in Queensland if applicable.

Ethics

Ethics approval for this evaluation was granted by the Human Research Ethics Committee of Queensland Department of Health, approval number HREC/14/QRCH/61/AM01. Research governance authorisation and site specific authorisation was obtained from Queensland Health (QH), as well as ethics approval from the Australian National University Human Research Ethics Committee.

Epidemiology and public health importance of hepatitis A in Queensland 1988-2014

From 1992-1999, there were in excess of 400 notifications of HAV per year in Queensland but since 2009 there have been less than 50 notifications per year (Figure 5.1). There has been a substantial decline in HAV notifications coinciding with the introduction of the vaccine program for Aboriginal and Torres Strait Islander children in North Queensland in 1999. In 2009 there was a multi-state outbreak of HAV related to consumption of semi-dried tomatoes, however this had minimal impact on overall HAV notifications.

Figure 5.1:   Hepatitis A notifications in Queensland, 1988-2014.
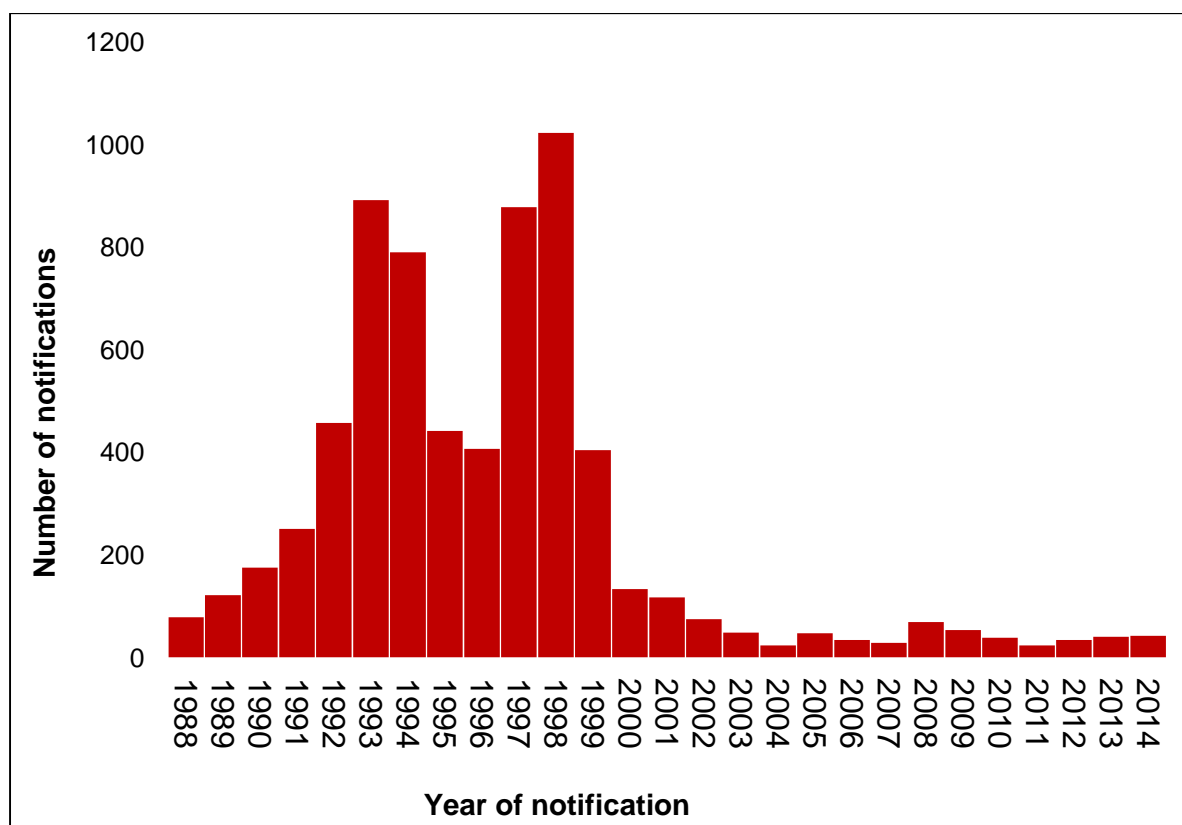
My analysis of the data indicated the most common age group affected from HAV in Queensland to date are those between five and 40 years old. Previously the most likely mode of HAV transmission in Queensland to children was from common source outbreaks in childcare facilities.[7] My analysis (see *Results* section) found that most notified cases in Queensland now occur following international travel or contact with a returned traveller. Over time there has been a definite shift in the mode of transmission of acquiring HAV from that of common source outbreaks to overseas travel.

Current hepatitis A surveillance system in Queensland

The Queensland Notifiable and Other Conditions System (NOCS) operates as a passive surveillance system. Clinicians and laboratories are required to notify public health units (PHU) of probable and confirmed diagnoses of HAV under the *Queensland Public Health Act 2005*.[5] Once the HAV notifications are received from laboratories and clinicians, they are recorded in the NOCS. All HAV notifications are actively followed-up by the Public health Units (PHU), which all have access to NOCS. There are three major pathology providers who

manage more than 90% of HAV notifications in Queensland. All three providers notify HAV to Queensland Health electronically, resulting in efficient and timely reporting.

Case definition

The Australian National Notifiable Disease Surveillance System (NNDSS) provides the case definition for HAV which was implemented and updated by the Communicable Diseases Network Australia (CDNA) on 01 January 2013.[10] The current national case definition is outlined in Table 5.2 below.

The CDNA developed this case definition to enable a nationally standardised approach in Australia for the surveillance of HAV.[10] The data are collected by all states and territories in Australia under their own jurisdictional public health legislation, and are reported to state and territory notifiable surveillance systems. OzFoodNet (OFN) is a national collaboration for enhanced surveillance and follow-up of enteric pathogens, which includes HAV. Hepatitis A positive cases are followed up by the jurisdictional health authorities with regular uploads of de-identified data from the state and territory-based databases provided directly to the NNDSS. Data are collected, analysed and reported back to relevant stakeholders on a fortnightly basis with quarterly reports documenting trends from notified cases of HAV in Australia.

Table 5.2:   **National Notifiable Disease Surveillance System case definition for hepatitis A, 2013.**

Confirmed case	Laboratory definitive evidence OR Laboratory suggestive AND clinical evidence OR Laboratory suggestive evidence AND epidemiological evidence
Probable case	A probable case requires clinical evidence AND epidemiological evidence
Laboratory definitive evidence	Detection of hepatitis A virus by nucleic acid testing
Laboratory suggestive evidence	Detection of hepatitis A-specific IgM, in the absence of recent vaccination
Clinical evidence	Child less than 5 years of age OR acute illness with discrete onset of at least two of the following signs and symptoms: fever; malaise; abdominal discomfort; loss of appetite; nausea AND Jaundice or dark urine or abnormal liver function tests that reflect viral hepatitis.
Epidemiological evidence	Contact between two people involving a plausible mode of transmission at a time when: a. one of them is likely to be infectious (from two weeks before the onset of jaundice to a week after onset of jaundice) AND b. the other has an illness that starts within 15 to 50 (average 28 – 30) days after this contact AND At least one case in the chain of epidemiologically linked cases (which may involve many cases) is laboratory confirmed.

Purpose and objectives of the HAV surveillance system

The purpose and objectives of the current HAV surveillance system in Queensland are not specifically stated. I have assumed that the purpose is to capture complete data on HAV notifications in Queensland in a useful way to then inform policy and practice. In order to achieve this, the NOCS system needs to be able to:

- Monitor trends in a timely way;

- Detect changes that may indicate any increase in disease among high-risk groups and or any change in risk factors for the disease;

- Assess the success of prevention and control measures; or

- Instigate further research on the disease.[11]

In the absence of documented objectives of the current HAV surveillance system in Queensland, I set the following specific objectives for my evaluation:

- Assess the surveillance system attributes of NOCS in relation to HAV;

- Appraise current stakeholder engagement with the NOCS system;

- Analyse and describe HAV notification data in order to 1) monitor trends over time and 2) establish whether the surveillance system had the capacity to assess whether endemic HAV transmission had been interrupted in Queensland;

- Describe the limitations of the current system and provide recommendations.

Methods

This chapter follows the structure of the framework used by Teutsch and Churchill[11] and the Centers for Disease Control updated guidelines for evaluating a public health surveillance system.[9] As such, this chapter does not contain a traditional discussion section; instead I have opted to include the discussion within the results section and a summary post results. I have done so to enhance the readability of the evaluation.

System attributes

Due to the scope of this project, the key system attributes assessed for this evaluation were: sensitivity and acceptability; timeliness; representativeness and data quality (Table 5.3). Other surveillance system attributes are also shown in Table 5.3 and were considered in the evaluation.

In relation to sensitivity, I focused on the sensitivity of the HAV surveillance system as opposed to sensitivity of testing methods or sensitivity of genotyping (a test which has high sensitivity and specificity). Sensitivity of the HAV surveillance system is a measure of how well the proportion of true HAV cases in Queensland are being identified by the HAV surveillance system.[12]

Reviewing characteristics of the population from multiple sources of data can assist in measuring trends, in revealing important findings and can be used as an indicator of the *representativeness* of the HAV surveillance system data. Notification data from the NOCS system and OFN dataset were analysed according to person, place and time. Completeness of data *(data quality)* was assessed as part of the detailed data analysis for the NOCS system, OFN database and genotype dataset (received from QHFSS laboratory). An audit was conducted comparing paper based case report forms with existing data fields in the NOCS database. Enhanced HAV surveillance data from OFN and genotype data from QHFSS provided further details on locally acquired cases.

Table 5.3:   Hepatitis A surveillance system attributes in Queensland

Attribute	Description of attribute and questions asked in stakeholder interviews
Simplicity	Whether the structure of the system flows easily and is operationally uncomplicated. Low resource requirements for case follow up and contract tracing.
Flexibility	Adaptable to any changing reporting requirements or novel methods of data collection and analysis such as laboratory methods and genotype data.
Acceptability	Whether stakeholders are engaged in the system. This will be reflected in high rates of hepatitis A being reported in a timely way as well as completeness of questionnaires from interviews and report forms.
Sensitivity	Are case reports being completed in order for the system to detect changes in disease occurrence in the community? Is the system designed to detect hepatitis A outbreaks?
Predictive value positive (PVP)	Whether the system provides confidence by precluding low false-positive results, avoiding overestimating the level of immunisation coverage or using valuable resources.
Representativeness	Analysis of hepatitis A notifications from the NOCS system that specifies time, place and person data to determine whether the sample is representative, in particular Aboriginal and Torres Strait Islander identity.
Timeliness	Whether data are available in a timely way or are there delays in any steps from data notification to receiving reports? How acceptable is a delay in notification?
Data quality	Who is responsible for the quality of data? How are inconsistencies of data managed? Are validation checks of the data performed at any stage?
Stability	Whether there are adequate resources, such as costs associated with staff as well as the collection and maintenance of the operational system.

Stakeholder Engagement and Consultation

Stakeholder interviews were conducted with current HAV surveillance system users identified in Table 5.4. The purpose of these interviews was to determine the level of engagement with the system, seeking opinions about the system attributes including acceptability and timeliness. A short questionnaire with a series of closed and open ended questions was developed for this task and responses were categorised into common themes.

Table 5.4:   Stakeholders involved in evaluating the hepatitis A surveillance system in Queensland

National Notifiable Diseases Surveillance System (NNDSS)
OzFoodNet (national and Queensland epidemiologists)
The following Queensland Health employees:
Epidemiologists
Immunisation providers
Data managers (providers and users)
Public health practitioners, physicians and nurses
Acting director of a public health unit
Queensland Health Forensic Scientific Services laboratory scientists
Queensland Health Public Health Virology
NOCS users
NetEpi data users

Stakeholders approached for interviews were those responsible for: (a) conducting case interviews, (b) data collection and entry of data, (c) data generation from NOCS for the purposes of producing reports, (d) interpretation and dissemination of the data. Other relevant stakeholders approached for interview consisted of personnel responsible for; managing the reference laboratory in Queensland where HAV positive samples are tested, genotyped and entered into an international database. OzFoodNet epidemiologists and Queensland Health (QH) epidemiologists were also interviewed.

Data analysis

I analysed retrospective HAV notification data for the period 1988 to 2014. I analysed three datasets: (a) the NOCS dataset on HAV notifications, and (b) the OFN enhanced surveillance data and c) the QHFSS genotype data. I used summary statistics (counts, proportions) to describe HAV epidemiology using available demographic and risk factor data. These

included age, sex, vaccination status, Indigenous status, mechanism of infection, history of travel or exposure to a returned traveller, exposure to a known case, child care or school attendance or living with a child who attends childcare or school (Table 5.5). Where relevant, I also determined the prevalence of risk factors known to be associated with increased HAV risk.

Table 5.5:   Retrospective case series data available for analysis of hepatitis A notifications, Queensland 1988-2014

Study population	All probable and confirmed cases of hepatitis A infections from the Queensland NOCS System database and OzFoodNet enhanced surveillance data from January 1st 1988 to 10th May 2014
Risk factors	Travel history, exposure to a known case, child care and/or school attendance, living with a child who attends child care and/or school, mechanism of infection, MSM, IVDU and food exposure, vaccination status, Indigenous status
Outcome measures	Hepatitis A virus notifications (i.e. PCR, serum) genotype, locally acquired, overseas acquired country of acquisition, Indigenous status, NHIG recipients, hospitalisations, deaths
Covariates	Sex, age, Indigenous status, vaccination status

I merged the OFN enhanced surveillance data with the NOCS database using the v-look up function in Microsoft Excel. I arranged the data so that each notification was recorded in a single row together with OFN enhanced surveillance data where applicable. Further data cleaning was conducted to identify duplicate results and illogical data entries such as dates, ages and other outliers. This final dataset of 6748 unique notifications was then manually audited for accuracy of merged data. Missing data were coded as such.

In addition, I analysed the available genotyping data to assess whether Queensland was in an elimination phase of HAV transmission – that is, if there is the absence of a common circulating genotype of HAV in Queensland. Genotyping of HAV notification data is now performed routinely through the Queensland Health Public Health Virology (QHPHV) laboratory in Brisbane. Genotyping data were provided by QHPHV laboratory from January 1

2002 to December 31 2014 in the form of a phylogenetic tree. I entered the data from the phylogenetic tree into Microsoft Excel in order to sort by genotype, year and country of acquisition. I recoded and grouped the country of acquisition data into world regions according to the World Health Organization (WHO) classification. The methods for conducting the genotyping are outlined in Table 5.6.

Table 5.6:   Hepatitis A genotyping methods undertaken at Queensland Health Public Health Virology laboratory, Brisbane, 2002-2014

Samples	2002-2006	2006-2013	2014-2015
Samples at FSS extracted with:			
• QIAamp® Viral RNA Mini Kit (Qiagen)	✓		
• Qiagen Universal Biorobot® system using the QiaAmp One-for-all Nucleic Acid kit or the Qiagen EZ1, using the EZ1 Virus mini kit v2.0		✓	✓
RT-PCR performed using:			
• a 2-round assay using primers published by Grinde et al 1997	✓	✓	
• a single round of PCR with primers published by Faber et al 2009.			✓
PCR products screened using:			
• gel electrophoresis, with the expected size of 397bp	✓	✓	
• QIAxcel® and any detected were run on gel electrophoresis			✓
• Bands were excised from the gel and purified using the QIAquick® Gel Extraction kit.		✓	✓
Sequencing:			
• set primers HAV8 and HAV9 using the Big Dye terminator kit v3.0	✓	✓	
• performed on an ABI 3130xl Genetic Analyser	✓	✓	
• set primers HAV6a, HAV6b, HAV17a and HAV17b, using the GenomeLab DTCS Quick Start kit			✓
• performed on the CEQ8000 genetic Analysis System using the standard LFR-1 program			✓
• Contigs assembled in Sequencher 5.0 and phylogenetic analysis conducted using the MEGA5 program			✓

Source: Judy Northill QHPHV, May 2015

Results

System attributes

Results from analyses of stakeholder interviews were incorporated within the assessment of the system attributes. These include results from the detailed data analysis of notification and OFN enhanced surveillance data.

Sensitivity

The true sensitivity of the HAV surveillance system is unknown. Stakeholders who were interviewed stressed that as a passive surveillance system with low numbers of HAV infections each year, the key aspect with regard to sensitivity was the capacity to monitor increases in locally acquired HAV notifications in Queensland. In the event that a locally acquired HAV case is identified, the standard protocol for follow-up by public health units includes active case ascertainment.

The results from the data analyses of HAV notifications in Queensland from 1988-2014 showed that, where there *has* been a risk factor recorded in the NOCS dataset, the majority of notifications indicate disease acquisition was associated with overseas travel or exposure to a returned traveller. These overseas acquired infections ensued from travel to countries where HAV is still endemic. However, a considerable proportion of HAV cases in the NOCS system have either missing data or no risk factors recorded for the source of locally acquired infections (Figure 5.2). Known risk factors include intravenous drug use (IVDU), men who have sex with men (MSM) and exposure and consumption of high risk foods such as shellfish. The analysis indicates the sensitivity of the surveillance system is compromised because poor data quality inhibits the capacity to adequately identify risk factors for locally-acquired HAV infections and to monitor changes in trends over time.

Figure 5.2:   Identified risk factors recorded for hepatitis A infections, Queensland 2001-2014
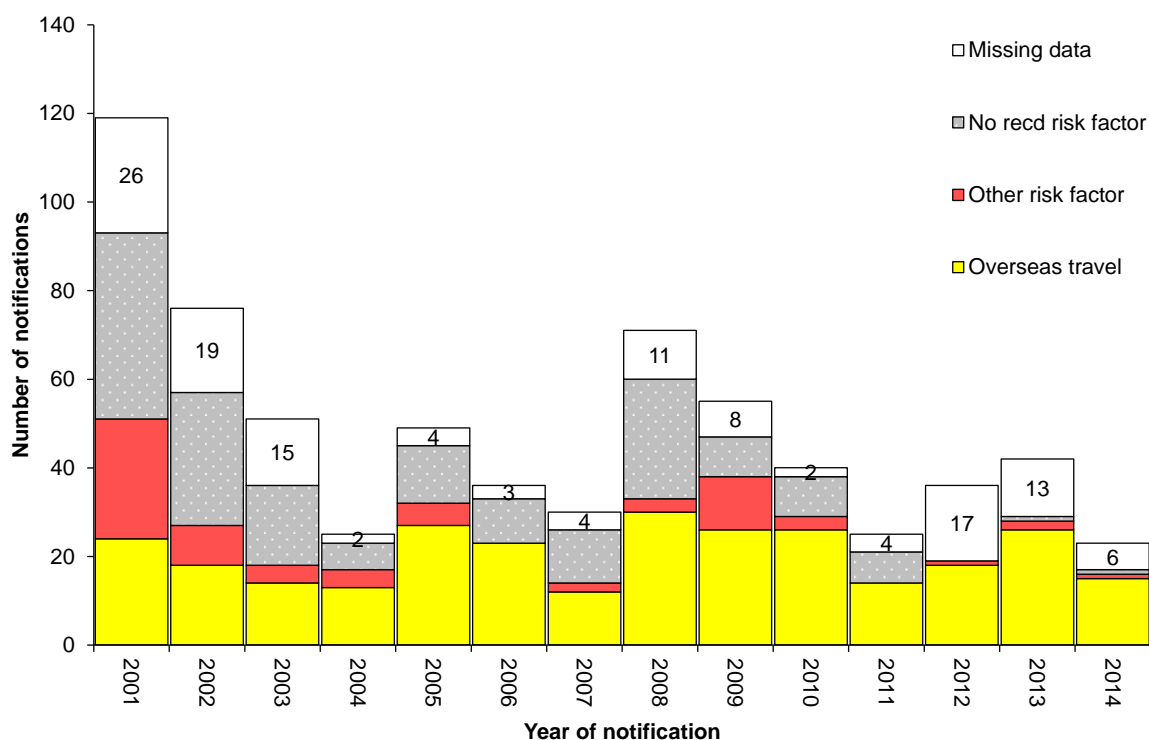
Acceptability

Whether stakeholders are engaged in the system is reflected in high rates of HAV being reported in a timely way, as well as completeness of questionnaires from interviews and report forms. OzFoodNet staff reported that the current system works very efficiently. At a national level, reports are received from Queensland OFN members fortnightly, quarterly and annually in addition to reports received at face to face meetings. Queensland system users report to NNDSS with case information as necessary and there is direct liaison with the state reference laboratory (QHFSS) when there are outbreak investigations occurring.

During stakeholder discussions, concerns were raised from some users regarding the security and privacy of currently uploading all HAV genotype sequencing data into the international HAV.net database. Other concerns were raised regarding the level of communication between the different sections of Queensland Health who utilise the HAV surveillance system. There have been regular changes in virology laboratory personnel. This

has impacted on the communication between the virology laboratory and public health units and OzFoodNet. Staff will need to be updated with who the relevant virology laboratory personnel are in order to establish and continue the sharing of relevant information. Re-establishment of these relationships is required. Data quality regarding travel history in case report forms is another concern. The current variable for capturing travel history is inconsistent between case report forms (questionnaires) and required fields in the NOCS database. Travel information is also not being exchanged between the PHU, laboratory and OFN therefore important travel history is being lost. This makes the travel history data unreliable and inaccurate.

An important finding was considerable inconsistencies between the questions on the case report form and data fields in the NOCS database. Based on my analysis of the HAV notification data it was apparent that there were large amounts of missing data in the NOCS database for some variables, including dates in particular. However the questions related to these missing data were not actually included on the case report forms so the issue is not that the data were missing but that the data had no systematic way of being collected.

Timeliness

Timeliness is critical in a surveillance system to minimise ongoing transmission of HAV illness. Figure 5.3 summarises the key phases beginning from the presentation for medical care by the person infected with HAV. Stakeholders reported minimal delays between these steps and in the case of an outbreak or other urgency, time frames for particular steps of the notification process can be dramatically reduced to allow a timely and well informed public health response. OzFoodNet stakeholders email surveillance reports to relevant users of the HAV system fortnightly to ensure accountability and thorough follow up of cases. The phases where timeliness is considered fundamental to the surveillance system's success for HAV in Queensland are highlighted in Figure 5.3.

Figure 5.3:   Flowchart of hepatitis A surveillance system in Queensland demonstrating key phases in timeliness

| Presentation to health care facility following development of symptoms of hepatitis A. Treating physician orders pathology testing |
| HAV cases not identified (asymptomatic and not tested) or (symptomatic and do not seek medical care/are not tested) |

Laboratory tests conducted. Results referred back to treating physician

Case test positive (confirmed case)

Notification to PHU of probable and confirmed cases

OzFoodNet Qld notified

+/- Genotyping at FSS

Contact tracing and offer of vaccine if appropriate or Immunoglobulin if appropriate

Case interviews conducted. Case report forms completed

OzFoodNet Qld report confirmed cases to National OzFoodNet epidemiologist

Results of genotype sequence entered into Auslab and Hav.net international database

Data entered into NOCS database

Weekly epi report generated

Data entered into NetEpi and NNDSS databases

Data analysis

OFN produce fortnightly, quarterly and annual reports

*Shaded boxes indicate key phases of timeliness in hepatitis A notification process

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Discussions with laboratory stakeholders centred around the timeliness of genotyping data. The QHFSS reference laboratory in Brisbane is one of two laboratories in Australia who perform polymerase chain reaction (PCR) testing and genotyping for HAV. Methods are not standardised between the two laboratories. Victorian Infectious Diseases Reference Laboratory (VIDRL) are the other laboratory and this laboratory does not use the same sequences or target the same genes for genotyping as QHFSS, however QHFSS do the same sequencing as all international laboratories so that comparisons can be made between countries.[13] Queensland Health Forensic Scientific Services enter all HAV positive results that have been genotyped from returned overseas travellers into the international HAV database where comparisons of sequences can be made. Some private laboratories and interstate laboratories refer samples for genotyping or PCR testing to QHFSS.

Some faecal samples are referred to QHFSS for diagnostics purposes (for PCR and genotyping) or from public health medical officers as part of an outbreak investigation looking for epidemiologically linked cases. Not every sample will be genotyped, particularly if there are several members from the same family with clear epidemiological links. This is due to the cost of testing and the amount of time and resources required to perform the testing.

Most genotyping is done in batches. Urgent requests from a public health unit for genotyping and PCR of single samples can be completed within 24 hours from receipt of the sample. Typically, the genotyping and sequencing data become available one to four weeks following specimen receipt at QHFSS. The batching process alone can take up to one week to complete but is preferred due to the costs and human resources required to complete testing. Results are reported to OFN and to PHU's in an ad-hoc fashion. The data are entered into the NOCS and OFN databases "irregularly".

Data quality and representativeness

Data analysis

There were 6748 single laboratory notified HAV cases extracted from the NOCS database for the period 1 January 1988 to 1 May 2014. OzFoodNet enhanced surveillance data for 192 laboratory confirmed notified cases of HAV from 2006-2014 were included in the analyses. These notifications came from a total of 16 PHUs within Queensland.

Age and sex data were 99% complete. The median age of cases was 25 years (range: less than one year to 97 years), 58% of all notifications were male. The age-sex profile was typical of what would be expected in a setting where endemic HAV transmission has been interrupted, suggesting that the notification data are representative of the HAV cases in Queensland for this time period.[2]

In contrast to age and sex, the risk factor data were largely incomplete. Examples of incompleteness of data are provided below. Data quality for travel history, post exposure prophylaxis (PEP) vaccination, Indigenous status, mechanism of infection in the form of risk factor data and hospitalisations were poor.

Travel

There are currently no routinely collected data by the NOCS system for interstate travel. Data on overseas travel is collected but entered as free text and not easily analysable, particularly with cases often travelling to one or more countries where HAV endemicity is high. OzFoodNet collects detailed information on overseas and interstate travel, however the format of data entered into their database is also free text and not easily analysable. The available data indicated that of 608 people who provided information on travel, 286 (47%) had travelled overseas. Of 147 cases from the OFN enhanced surveillance database with information on interstate travel, 14 (8%) reported interstate travel in the incubation period.

Post Exposure Prophylaxis

In Australia, PEP for HAV includes the administration of Normal Human Immunoglobulin (NHIg) or hepatitis A vaccine given within two weeks of last exposure from an infectious case or source of infection.[14,15] If NHIg is given according to these recommendations it is of more benefit in controlling community wide outbreaks particularly if given as soon as possible.[16] In the NOCS database, 436 (6%) of HAV positive cases received one or more doses of NHIg but, due to incomplete data, the reason why NHIg was given, or not given, remains unclear.

Mechanism of infection/risk factors for infection

The HAV surveillance system seeks to ascertain mechanisms of infection as potential factors for acquiring HAV: childcare workers, person-to person and foodborne-related infections. Of the 6748 HAV notifications, a maximum of only 570 had any data recorded on these risk factors:

- Childcare worker 45/570 (8%);
- Person-to-person transmission 63/524 (12%); and
- Foodborne related infections 125/501 (25%).

Intravenous drug use (IVDU)

Data collection for IVDU was poor within the HAV notification dataset. Of the 6748 notifications to PHU across Queensland, 91% had data missing for this variable. Of the 559 cases where the data were collected, only 1% identified as using intravenous drugs. Other Australian data suggest close to 25% of HAV infected persons are intravenous drugs users.[17-19]

Men who have sex with men

Data collection on MSM was poor for HAV notifications. Of the 6748 notifications to the PHU across Queensland, 92% had data missing for this variable. Data were collected in 543 cases and of these cases, 3% of men identified as being a MSM. Other Australian data suggest close to 60% of male cases with HAV infections have sex with other men.[17-19]

Indigenous status

A process evaluation on the quality of the NOCS system data for HAV from 1991-2001 was conducted in 2002.[20] The report expressed concern regarding the large volume of missing data (89%) for the Indigenous status identifier. My analyses showed that missing data remained a major issue with 69% of the 6748 notifications to the public health units across Queensland having missing data on Indigenous status for the period 1988-2014. Of the 2084 cases where Indigenous status data were collected, 28% of people identified as being Aboriginal and or Torres Strait Islander (Figure 5.4). It is unclear whether there is a real over-representation of Aboriginal and Torres Strait Islander people in these notifications due to the large volume of missing data for this variable. This percentage (28%) is substantial, particularly considering Aboriginal and Torres Strait Islander people make up 3% of the total Australian population and 4% of the total Queensland population.[21] The establishment of the funded vaccine program in North Queensland for Indigenous children is likely to have contributed to a reduction in cases of HAV in the Aboriginal and Torres Strait Islander population, particularly in North Queensland.[7] Data quality has improved slightly for the variable Indigenous status since 2002 which is reflected in Figure 5.4 below.

Figure 5.4:   Aboriginal and/or Torres Strait Islander status of confirmed hepatitis A, Qld 1988-2014
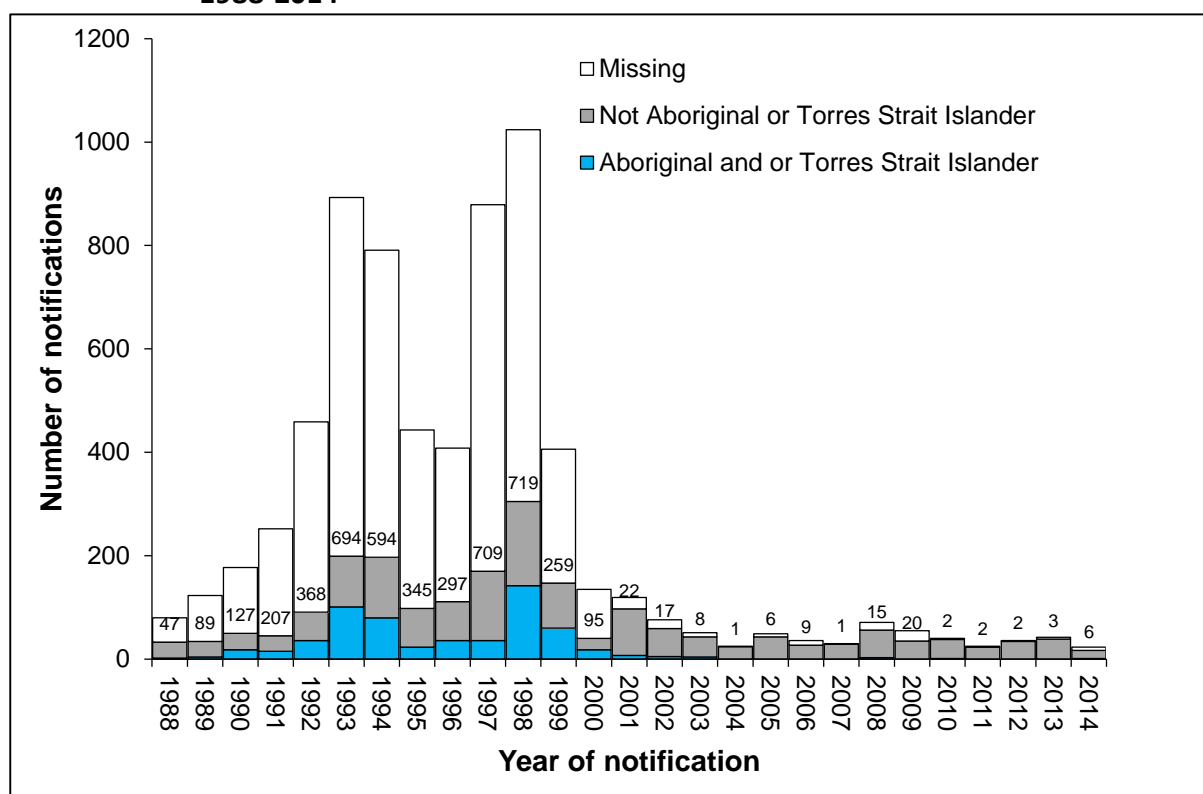
* Absolute values of missing data are shown in this figure

Morbidity and mortality

Prior to 2001, there were no recorded hospitalisations in NOCS associated with HAV infection. Morbidity and burden of disease for hospitalisations as a direct result of HAV infection was therefore not quantifiable for that period. From 2001 onwards, most data are missing for the variable 'hospitalisations' and 'deceased date'. For the available data, total hospitalisations recorded were 158/450 (35%) and there were a total of 15 deaths recorded. Mortality in Australia from HAV is low.[22] In Queensland, deaths that occur directly as a result of a notifiable disease such as HAV are not required to be formally notified. As a result, the combination of these two factors is reflected in the large volume of missing data in NOCS for the variable 'died of condition'.

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Genotype data

There are seven unique genotypes of HAV ranging from I to VII. Types IV, V and VI are believed to be isolated from simian species in captivity only and not in humans.[13] There were data for 152 genotype samples analysed from laboratory confirmed HAV cases in Queensland. Analysis of the phylogenetic tree data showed there were two (out of the possible seven) unique genotype strains identified. These strains were I (A and B) and III (A). The most prominent genotype strain of HAV in Queensland since 2002 was IA (62%), followed by IB (26%) and 3A (12%) as shown in Figure 5.5.

Figure 5.5:   Hepatitis A genotypes by year of notification in Queensland, 2002-2014
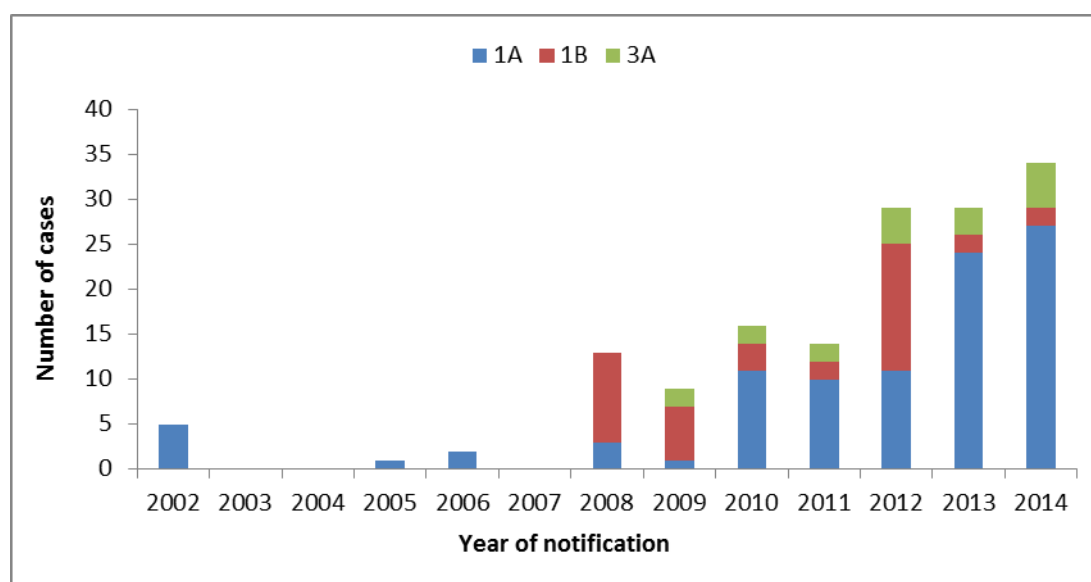
Genotype data are analysed in the QHPHV laboratory. When stakeholder interviews were conducted, personnel indicated travel history data were often incomplete, missing or recorded as 'unknown'. Where this was the case, the place of acquisition was auto-recorded as 'Queensland' regardless of accuracy. One limitation of the data is that they are not linked with the NOCS dataset so it is not possible to determine an accurate country of origin for each genotype result. Unique laboratory identification numbers are different to the unique identification number allocated through the NOCS system and a data linkage process would need to be undertaken for this type of analyses.

An analysis of country of acquisition of infection from these genotype data (Figure 5.6) demonstrated a combination of local and imported cases. However due to the inaccuracy of travel history data and allocation of 'Queensland' as the chosen source of acquisition in the absence of available travel history, the usefulness of these data must be questioned.

Figure 5.6:   **Hepatitis A genotypes by location of origin of infection, Queensland, 2002-2014**
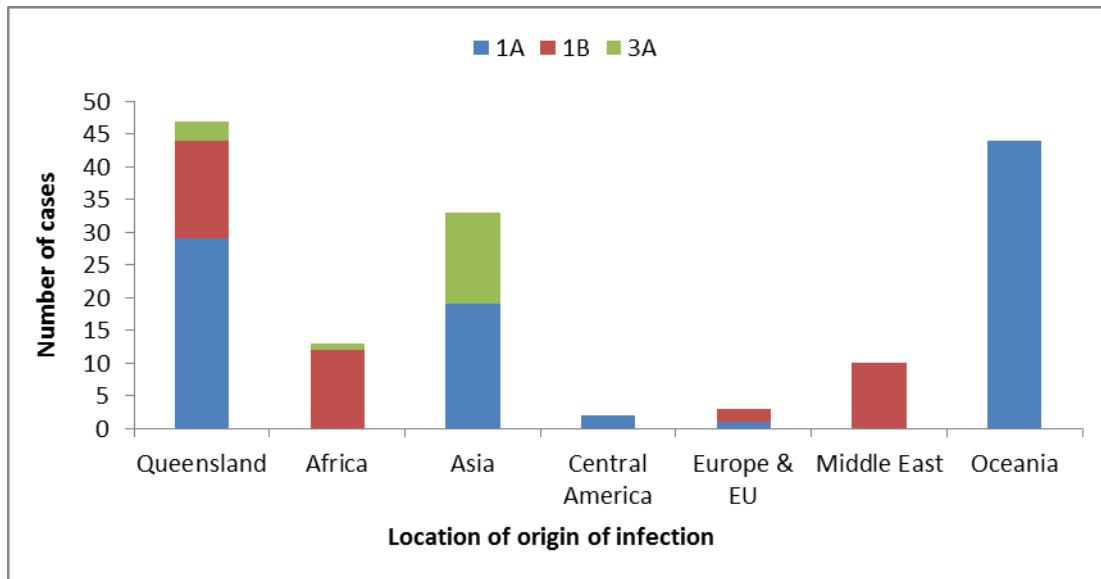
Summary

Adequately functioning public health surveillance systems are essential in order to recognise outbreaks and changes in trends of infectious diseases. The history of closing the gap with respect to the burden of hepatitis A amongst Aboriginal and Torres Strait Islander peoples in Australia is a good news story in which Queensland has played a pivotal role. As this disease burden appears to be declining, there are challenges for the current hepatitis A surveillance system in Queensland. Some key areas where there is scope for improvement include:

- Streamlining the NOCS database to accurately reflect the questions being asked in the case report forms.

- Quality assurance checks in the current NOCS database for completeness of data; particularly Aboriginal and Torres Strait Islander status, risk factor data and mechanism of infection. This includes following up and updating travel history data.

- Inclusion of Aboriginal and Torres Strait Islander status on all laboratory and reporting request forms. There is not the capacity to collect these data on current forms therefore under-identification will continue to remain an issue.

To perform at its desired level, the limitations observed as a result of this evaluation would need to be addressed.

Recommendations

In order to improve the usefulness of the Queensland NOCS surveillance system for HAV notifications, the following actions are recommended:

High priority

1. Standardise the Queensland case report form for HAV to match the data fields in the NOCS database for consistency and accuracy of data. Ensure all options are available for responses so there is no room for personal interpretation and to minimise missing data.

2. Create a continuous quality improvement feedback system to minimize missing data from case report forms and data fields in the NOCS system. Generating weekly lists for follow up of missing data for those responsible for data at all levels.

Medium priority

3. Improve the communication between PHU's, OFN and QHPHV unit regarding updating details of travel history data in the current system.

4. Advocate for the addition of Aboriginal and Torres Strait Islander status on all official documents related to notification data such as laboratory request forms.

Lower priority

5. Link the NOCS dataset with the genotype dataset to better distinguish between locally acquired and imported cases of HAV. There is potential for this to complete the surveillance loop if the results for the genotype data were to be systematically entered into the NOCS database.

6. Develop and implement an education strategy for staff interviewing cases regarding risk factor data. Asking and recording the questions surrounding Indigenous status, IVDU and MSM status is imperative for improving data quality, particularly where the source of infection is unknown.

Conclusion

There has been a change in the landscape over time for HAV notifications in Queensland. What were predominantly foodborne related infections and much higher numbers of Aboriginal and Torres Strait Islander people now have been replaced by a reduction in local endemicity where most cases are acquired as a result of overseas travel or exposure to a returning overseas traveller. The establishment of the funded vaccine program in North Queensland contributed to a reduction in cases of HAV in Aboriginal and Torres Strait Islander people. It is unclear what vaccine uptake is like in the private sector which was outside the scope of this evaluation, however improved vaccination rates in prospective overseas travellers in all areas of health care provider service could reduce current case numbers even further.

Regarding the current HAV surveillance system's functionality; the timeliness of all aspects of the current system is reassuring as notifications are managed and processed within appropriate time frames. There needs to be a sustained improvement in completeness of data at every step for identification of Aboriginal and Torres Strait Islander people and for risk factor data. Whether data from the current NOCS surveillance system is representative of cases occurring in Queensland is unreliable due to the large volumes of these missing data.

Finally, this evaluation of retrospective case series data from the Queensland NOCS surveillance system may be of interest to clinicians, researchers and vaccine providers locally and interstate who may be further encouraged to continue to offer a targeted prevention strategy of vaccination in at risk populations.

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Appendix 5.1.   Communicable Disease Control (CDC) conference presentation, Brisbane, June 2015
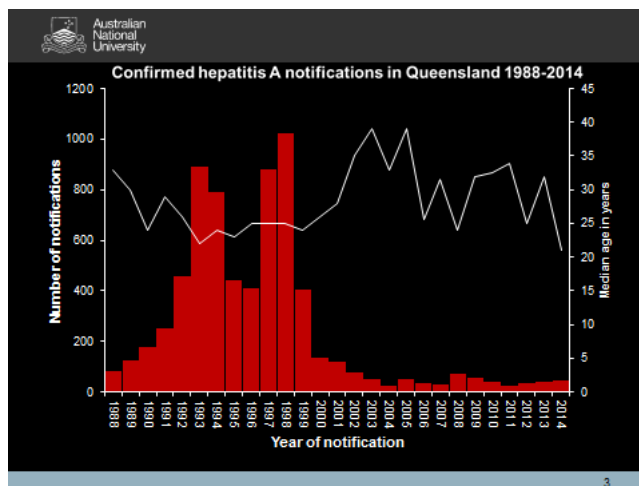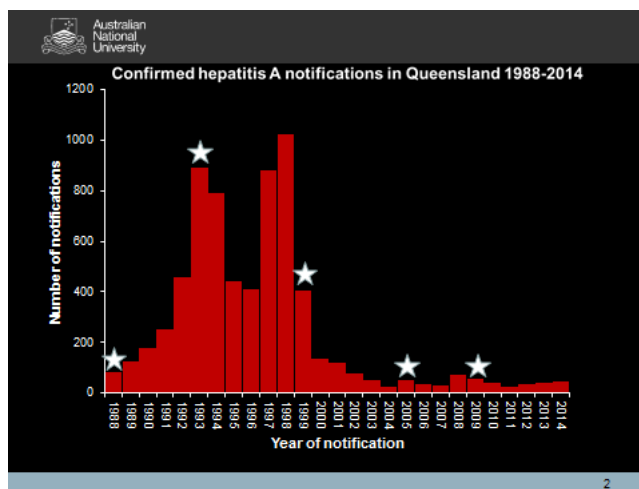
6.   *Teaching: Lesson from the Field and Teaching session for the 2015 MAE cohort as part of the Outbreak Investigation course*

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Prologue

A core competency of the MAE program is to conduct a teaching session on an aspect of epidemiology to the MAE cohort of the following year. This was completed during our third courseblock in March 2015. Collectively our MAE 2014 cohort assisted in the running of the "Outbreak Investigation" session which involved my half of the group acting as 'roving helpers' or tutors during the EpiInfo data analysis section.

The other component of our teaching session competency centred on our cohort dividing into three groups of three in order to establish themes and structure for a more tailored teaching session to the MAE 2015 cohort. My group decided on bias, with a focus on Aboriginal and Torres Strait Islander health data as we all had existing knowledge regarding the limitations in this area.

I didn't realise how much planning and effort goes into a one-hour teaching session! Mahomed Patel provided us with valuable, constructive feedback for this teaching session and I would personally like to acknowledge and thank him for his enthusiasm and time in helping us with its refinement. This was a really fun and worthy opportunity to engage with the next cohort of MAE scholars.

During the data analysis component of my epidemiological project (FluMum birth outcomes), it became clear that there was an opportunity to use the results as part of my 'Lesson from the Field'.

There were numerous analyses showing highly statistically significant results however from clinical experience, I knew these were not clinically relevant and would not mean a change in public health practice.

Lesson from the Field

Statistical significance versus clinical importance: The role of 'absolute risk' and 'risk difference'

Learning Objectives

a) Describe 'risk difference' and the role it plays in the context of interpreting outcome results from a data analysis.

b) Calculate and interpret risk differences from Stata outputs using actual data analyses from a cohort study.

c) Discuss the relationship between statistical significance and clinical importance and how these can influence public health practice.

Background

Statistical significance and clinical significance are terms often used interchangeably but incorrectly.[1] Statistical significance is intended to determine whether the probability of results calculated from a study are due to chance or are in fact 'real' and may be replicated if the same study were to be repeated.[3] Clinical significance however, is determining whether results derived from a study are relevant enough to warrant a change in clinical practice or public health policy.[3] Clinical significance or clinically meaningful results are not necessarily linked with statistically significant results. Of course they might be, but it is more important to review a combination of results from an analysis to appreciate the whole picture before making inferences. Significant p-values or 95% confidence intervals that do not cross one, on their own do not automatically mean that the result is clinically important or of great public health value.[1] On the other hand, statistically insignificant results from data analyses do not necessarily mean the results are not clinically important or of great public health value either.[1]

That is when examining absolute risk and risk differences may be more meaningful when used alongside the more traditional significance tests as well as looking at the

results in context. It is important to remember that a relative risk is a measure of the strength of the association between a factor and a disease or outcome, however the risk difference provides a measure of the public health impact of the risk factor,[1] and traditionally focuses on the number of cases that could potentially be prevented by eliminating the risk factor.[1]

Scenario

The following scenario was provided to the 2014 MAE cohort.

FluMum is a national study that has the largest cohort of mother-infant pairs in Australia to date. Researchers investigated whether there were any differences in birth outcomes between women who received an influenza vaccine during their pregnancy compared to women who did not receive an influenza vaccine during their pregnancy within this cohort of 7125 mother-infant pairs from 2012 to 2014 inclusive. The primary exposure of interest was self-reported receipt of an influenza vaccine in pregnancy, and the primary outcomes of interest were infant birthweight in grams and gestation in weeks at birth of the infant.

Data analyses were performed using Stata v12 (StataCorp, Texas, USA). Data for both outcome variables were normally distributed hence two- sample t-tests were used for continuous variables and chi squares for categorical variables. Relative risks (RR) were calculated to determine any associations between the primary exposure of interest and each primary outcome. Levels of statistical significance were set *apriori* at p values of < 0.05 and 95% confidence intervals (CI's) that did not cross 1.

The baseline characteristics of study participants by receipt of vaccination during in pregnancy are presented in Table 6.1.

Table 6.1:   **FluMum study participants, by self-reported maternal influenza vaccination in pregnancy status, Australia (2012-2014)**

Variable	influenza vaccine in pregnancy (95% CI)		P value
	Yes **n= 2394**	**No** **n= 4732**	
Maternal age (mean, in years)	32.1 (31.9-32.3)	31.5 (31.3-31.6)	**0.000***
Mother Aboriginal and/or Torres Strait Islander	75 / 2393 (3%)	128 / 4725 (2%)	0.31
Weeks pregnant 1st Antenatal care	8.2 weeks (8.0-8.5)	8.8 weeks (8.6-9.0)	**0.0005***
Smoking in pregnancy	141 / 2392 (6%)	383 / 4726 (8%)	**0.0009***
Diabetes in pregnancy	229/ 2391 (10%)	364 / 4724 (8%)	**0.0061***
Any co-morbidity/flu risk factor	558 / 2393 (23%)	969/ 4726 (21%)	**0.0063***

Source: FluMum study data 01 April 2012-31 Dec 2014. CDC conference abstract, 2015

A discussion was held amongst the investigators and a decision was made to go no further with any multivariate or regression analyses related to these univariable results. Results from the univariate analyses showed there was no indication to do so.

The results of analyses of the primary outcomes were as follows:

a) Babies born to mothers who had an influenza vaccine during pregnancy had a mean birth weight of 3325 grams, compared to babies of mothers who did NOT receive an influenza vaccine during pregnancy whose mean birth weights were 3336 grams. This difference of 11 grams was not statistically significant or clinically important.

b) Mothers who had an influenza vaccine during pregnancy and mothers who did NOT have an influenza vaccine during pregnancy <u>both</u> had a mean gestation at delivery of 38.7 weeks. Clearly this was not statistically different or clinically important either.

There were however, some statistically significant results when examining for potential confounding variables such as maternal co-morbidities and risk factors for influenza. Students were then asked to view the .ppt doc FluMum Stata output examples.

Interpreting Stata outputs

Students were sent Stata outputs resulting from actual data analysis from the FluMum cohort study and asked to describe the results. All six results were statistically significant in terms of pre-determined levels set at a p value of < 0.05, and 95% CI's that did not cross 1. Some results were highly significant. Students were then asked to identify the risk difference in the Stata output, or alternatively calculate the risk difference using the calculation in Figure 6.1, and describe whether they thought the results were clinically meaningful, what the public health importance might be if any, and why.

Figure 6.1:   Calculation for risk difference

Risk Difference (RD) = (I_e) - (I_u)
where (I_e) = incidence among the exposed subjects,
and (I_u) is the incidence among unexposed subjects.

The risk differences were calculated for the following six Stata examples:

1. Mean maternal age in years at delivery of infant, by influenza vaccine given during pregnancy

```
***FLUMUM UNIVARIABLE ANALYSIS FOR LFF
```

```
. ttest Maternal age at delivery, by (Flu vaccine given in pregnancy )

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   (0)No |    4715    31.45961    .0788282    5.412808    31.30507    31.61415
  (1)Yes |    2389    32.12061     .103395    5.053677    31.91785    32.32336
---------+--------------------------------------------------------------------
combined |    7104     31.6819    .0629244    5.303601    31.55855    31.80525
---------+--------------------------------------------------------------------
    diff |            -.6609931    .1329688               -.9216516   -.4003346
------------------------------------------------------------------------------
    diff = mean((0)No) - mean((1)Yes)                              t =  -4.9710
Ho: diff = 0                                    degrees of freedom =      7102

    Ha: diff < 0                 Ha: diff != 0                  Ha: diff > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
```

Risk difference = -0.66.What does this mean?

ANSWERS: If we look at the p value and the 95% CI it certainly suggests there's a statistically significant difference but the real difference is only ~6months of age which isn't clinically important for this example. Large sample sizes are more likely to show a statistical significance between two groups particularly when numbers in the unexposed group are much less.[2]

2. Mean gestation in weeks at first presentation for antenatal care, by influenza vaccine given during pregnancy

```
. ttest weeks pregnant at first presentation for antenatal care, by (FluvaxPreg)

Two-sample t test with equal variances
------------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
   (0)No |    4727     8.80897    .0953766    6.557447    8.621987    8.995952
  (1)Yes |    2394    8.248538    .1240679    6.070457    8.005246     8.49183
---------+--------------------------------------------------------------------
combined |    7121    8.620559    .0758765    6.402913    8.471818    8.769299
---------+--------------------------------------------------------------------
    diff |             .5604317    .1604915                .2458206    .8750428
------------------------------------------------------------------------------
    diff = mean((0)No) - mean((1)Yes)                            t =    3.4920
Ho: diff = 0                                     degrees of freedom =      7119

    Ha: diff < 0                 Ha: diff != 0                  Ha: diff > 0
 Pr(T < t) = 0.9998        Pr(|T| > |t|) = 0.0005         Pr(T > t) = 0.0002
```

Risk difference = 0.56.What does this mean?

ANSWERS: As with the 1st example, the p value and the 95% CI suggest there's a statistically significant difference but the real difference is only part thereof a week, which again isn't clinically meaningful for this example. Again, large sample sizes are more likely to show a statistical significance between two groups in this example, due to the exposed group being much smaller than the unexposed.

3. Diabetes in pregnancy, by influenza vaccine given during pregnancy

```
Diabetes in pregnancy
              | Maternal flu vaccine  |
              | during pregnancy      |
              |  Exposed   Unexposed  |     Total
--------------+-----------------------+------------
        Cases |    231         366    |      597
     Noncases |   2162        4355    |     6517
--------------+-----------------------+------------
        Total |   2393        4721    |     7114
              |                       |
         Risk | .0965316    .0775259  |    .083919
              |                       |
              |     Point estimate    |  [95% Conf. Interval]
              |-----------------------+-----------------------
Risk difference |      .0190056       |   .0049274    .0330838
     Risk ratio |     1.245152        |   1.064041    1.457088
Attr. frac. ex. |      .1968849       |   .0601869    .3136998
Attr. frac. pop |      .0761816       |
              +-----------------------------------------------
                        chi2(1) =      7.46  Pr>chi2 = 0.0063
```

Risk difference = 0.02. What does this mean?

ANSWERS: 2% could be clinically important in such a large sample size. Is there potential bias though because women who are at risk (diabetics) will be targeted for flu vaccine in pregnancy anyway? This example could possibly be looked at more closely in a multivariable analysis or model.

4. Smoking in pregnancy, by influenza vaccine given during pregnancy

```
Smoking in pregnancy
                | Maternal flu vaccine  |
                | during pregnancy      |
                |   Exposed   Unexposed |     Total
----------------+-----------------------+------------
          Cases |     142         383   |       525
       Noncases |    2251        4338   |      6589
----------------+-----------------------+------------
          Total |    2393        4721   |      7114
                |                       |
           Risk |  .0593397    .0811269 |   .0737981
                |                       |
                |    Point estimate     |   [95% Conf. Interval]
                |-----------------------+-----------------------
Risk difference |       -.0217871       |   -.0340453    -.009529
     Risk ratio |        .7314436       |    .6071883    .8811267
  Prev. frac. ex. |      .2685564       |    .1188733    .3928117
  Prev. frac. pop |      .0903367       |
                +------------------------------------------------
                            chi2(1) =    11.03  Pr>chi2 = 0.0009
```

Risk difference = - 0.02. What does this mean? Is there a reasonable explanation for this?

ANSWERS: As above, -2% could indicate clinical importance in such a large sample size. Is there potential bias though because women who smoke are more at risk of respiratory illnesses and will be targeted for flu vaccine in pregnancy anyway? Or could there be a sample of participants who don't consent to be in the study due to their smoking status so will be under represented? Could women who are non-smokers be over-represented due to healthy volunteer bias? Does it really matter? No, but it's good to think about all possible reasons for your results, particularly potential selection bias!

5. Babies born prematurely, by influenza vaccine given during pregnancy

```
Babies born prematurely (under 37 weeks gestation)
                 | Maternal flu vaccine  |
                 | during pregnancy      |
                 |  Exposed   Unexposed  |     Total
-----------------+-----------------------+------------
          Cases  |     436         751   |     1187
       Noncases  |    1955        3961   |     5916
-----------------+-----------------------+------------
          Total  |    2391        4712   |     7103
                 |                       |
           Risk  |  .1823505    .1593803 |   .1671125
                 |                       |
                 |    Point estimate     |  [95% Conf. Interval]
                 |-----------------------+-----------------------
Risk difference  |        .0229702       |   .0042947    .0416456
    Risk ratio   |       1.144122        |   1.027759    1.273659
Attr. frac. ex.  |        .1259672       |   .0270095    .2148604
Attr. frac. pop  |        .0462693       |
                 +-----------------------------------------------
                            chi2(1) =     6.01  Pr>chi2 = 0.0142
```

Risk difference = 0.02. What does this mean? What might be a public health message here?

ANSWERS: Some might report this as 18% of women who had a flu vaccine in pregnancy had a premature baby. Timely to remember it is always important to report what the comparison is to the unexposed group (16%), which is very similar to the exposed. Some vocal campaigners have employed scare tactics using similar results in their reports (without showing the comparator).

6. Mean gestation in weeks at delivery, by mothers who had an influenza vaccine during the first trimester of pregnancy

```
*Look at primary birth outcomes (gestation & birthweights)between those mums who ///
> *had a flu vax in 1st trimester(Yes) compared to those mums who didn't have a flu
vaccine in pregnancy(No)
```

```
. ttest Gestation in weeks at delivery if GestTrimFluvax==1 | FluvaxPreg==0, by
(FluvaxPreg)
Two-sample t test with equal variances
-----------------------------------------------------------------------------
   Group |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+-------------------------------------------------------------------
   (0)No |    4720    38.70169    .0344223    2.364891    38.63421    38.76918
  (1)Yes |     142    38.29577    .1895767    2.259068    37.92099    38.67055
---------+-------------------------------------------------------------------
combined |    4862    38.68984    .0338835    2.362633    38.62341    38.75627
---------+-------------------------------------------------------------------
    diff |             .4059203    .2011646                .0115468    .8002938
-----------------------------------------------------------------------------
    diff = mean((0)No) - mean((1)Yes)                              t =   2.0179
Ho: diff = 0                                     degrees of freedom =     4860

   Ha: diff < 0                  Ha: diff != 0                  Ha: diff > 0
 Pr(T < t) = 0.9782         Pr(|T| > |t|) = 0.0437         Pr(T > t) = 0.0218
```

Risk difference = 0.40. What does this mean? What might be a public health message here?

ANSWERS: This result is not clinically meaningful regarding mean gestation in weeks at delivery of infants of pregnant women who received an influenza vaccine during their first trimester in pregnancy. It is safe for pregnant women to receive an influenza vaccine during the first trimester of their pregnancy with regards to prematurity.

Discussion Questions

The final part of the LFF was centred on discussion around our real life experiences related to publishing research.

1. When it comes to trying to publish your research, how do you manage statistically insignificant results that are clinically important, having been told journals rarely publish 'negative' findings?

   Responses: Once having selected the most appropriate journal for the paper, submit anyway including a great summary of descriptive epidemiological statistics with risk differences and the importance of the potential public health benefits.

2. How do you react to senior researchers who say your results won't get published unless you do multivariate analysis/modelling even though advice from your senior, experienced supervisors and a local biostatistician is that there is no indication to go ahead with any further analysis?

   Responses: a) In an ideal world you could change the study design to include a nested nested study and do a randomised controlled trial or case control study of that nested dataset

   b) do the multivariate/ modelling anyway to appease the masses

   c) don't do the multivariate/modelling and follow your supervisors' advice

   d) scratch your head and look confused

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2. Kirkwood B and Sterne J. *Essential Medical Statistics 2nd Edition*. Blackwell Publishing: Melbourne. 2008.pp150-155

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   www.med.uottawa.ca/sim/data/Statistical_significance_importance_e.htm

MAE Teaching Exercise

Bias in interpreting Aboriginal and Torres Strait Islander health data

Learning objectives:

a) Describe and interpret graphs commonly used in health data reports

b) Explain what bias is and the two major types of bias

c) Identify biases in Aboriginal and Torres Strait Islander health data

Appendix 6.1 includes slides used in this teaching session.

Exercise 1: The session started with a PowerPoint presentation showing graphs of the latest 'Close the Gap' national statistics on Aboriginal and Torres Strait islander health. We reminded the group there are three key elements we should consider when interpreting epidemiological data; chance, bias and confounding. We advised we would be focussing on bias for this teaching session.

We led the group through a refresher session on the two main types and potential sources of bias; selection bias and measurement bias to reinforce information the 2015 MAE cohort had recently learned at their first course block.

Exercise 2: The 2015 cohort were then split up into groups and asked to interpret the 'Close the Gap' graphs and whether they thought the results were 'real' with respect to being statistically significant. They were also asked to determine what types of biases were occurring in the Australian Bureau of Statistics (ABS) and Australian Institute of Health and Welfare (AIHW) child mortality graph provided and why. My MAE colleague Ana-Lena provided the graphs and data for this exercise and I was responsible for the development of the slides and proof reading.

Exercise 3: I was wholly responsible for the design and delivery of this third exercise. In this exercise we discussed the issue of under-reporting and incompleteness of Aboriginal and Torres Strait Islander status in health data and what are some of the implications when it comes to interpreting these data?

We discussed why under-reporting occurs, in which areas it occurs and the need to be cognisant of potential biases when it comes to interpreting Aboriginal and Torres Strait Islander health outcome data.

The group were led through two cases studies using real life examples of Stata outputs. These real life examples came from the data analysis component of two of my MAE projects and were:

1. Hepatitis A positive cases in Queensland 1988-2014 (unpublished data, 2015).
2. FluMum study; a national retrospective cohort study on birth outcomes, 2012-2014 (unpublished data, 2015).

These case studies were used to demonstrate poorly collected, incomplete data and an example of well collected complete data for the variable 'Indigenous status'. The group were asked whether these data are can be trusted, are they reliable and what are the implications of using these data in reports or in publishing them?

We also discussed the various stages of a research study in which measurement and selection bias can occur and how that can influence the internal and external validity of the study and hence the results. A 'tip of the iceberg' pyramid (provided in the slides) was also shown to reveal the different steps at which the identification process for Aboriginal and Torres Strait Islander people fails.

Recap: The group were asked to express key messages they had learned from our session and to list them from most important to least important. Following the responses we received from the 2015 cohort at the end of the session recap it was clear they had a firm grasp of how to interpret examples of health data and the concrete principles of bias. The 2015 MAE cohort also asked that a copy of our slides from the teaching session be uploaded onto their online learning platform 'Wattle'.

Feedback: This area proved to be an eye opener for some of the students whose responses in summary were [they]:

Had never really thought about the quality of health data presented in reports before, or that the data may in fact be incomplete which would lead to an under-representation of the total Australian population.

References used

1. Australian Government Close the Gap report, website accessed February 2015.

    https://www.humanrights.gov.au/sites/default/files/document/publication/CTG

    progress_and_priorities_report_2015.pdf

2. Australian Institute of Health and Wellbeing. National Mortality Database, accessed February 2015.

    http://aihw.gov.au/indigenous-statistics-quality-availability/#t2

3. Australian Bureau of Statistics website, accessed February 2015.

    http://abs.gov.au/ausstats/abs@.nsf/web+pages/statistics?opendocument#from-

Appendix 6.1- Presentation slides for MAE teaching exercise

Bias in interpreting Aboriginal and Torres Strait Islander Health data

Anna-Lena Arnold[1] Leone Malamoo[2] and Lisa McHugh[3]
MAE Scholars, National Centre for Epidemiology and Population Health
[1] Indigenous and Rural Health Division, Commonwealth Department of Health
[2] Australian Institute of Aboriginal and Torres Strait Islander Studies
[3] QCMRI & Communicable Diseases Branch, Queensland Health

At the end of this session you should be able to.....

- Describe and interpret a graph
- Explain bias and the two major types of bias
- To identify biases in Aboriginal and Torres Strait Islander health data
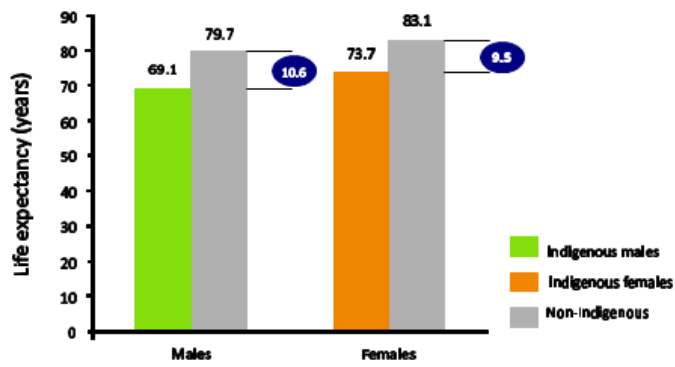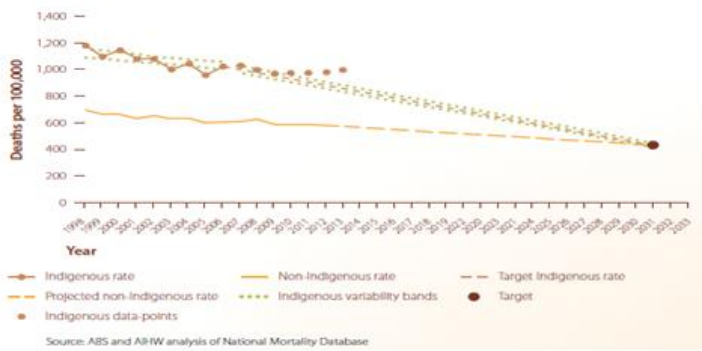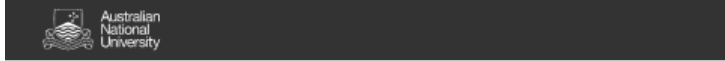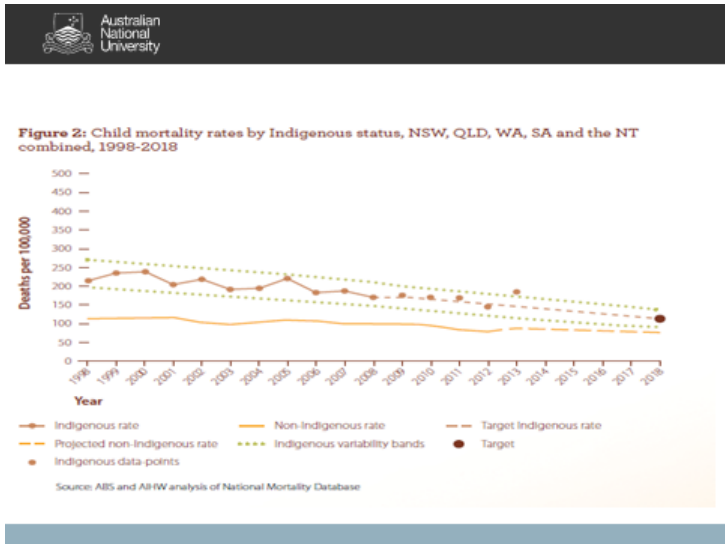
Life expectancy

Indigenous males: Males 69.1; Indigenous females: Females 73.7; Non-Indigenous: Males 79.7, Females 83.1; Gap Males 10.6, Females 9.5

Figure 1:
Overall mortality rates by Indigenous status: NSW, QLD, WA, SA and the NT combined 1998-2031.

Legend: Indigenous rate; Non-Indigenous rate; Target Indigenous rate; Projected non-Indigenous rate; Indigenous variability bands; Target; Indigenous data-points

Source: ABS and AIHW analysis of National Mortality Database

- Not on track to close the gap in life expectancy by 2031

Australian
National
University

Figure 2: Child mortality rates by Indigenous status, NSW, QLD, WA, SA and the NT combined, 1998-2018

Source: ABS and AIHW analysis of National Mortality Database

Australian
National
University

- On track to halve the gap in mortality rates for Indigenous children under five within a decade by 2018

Do you believe it?

Figure 2: Child mortality rates by Indigenous status, NSW, QLD, WA, SA and the NT combined, 1998-2018
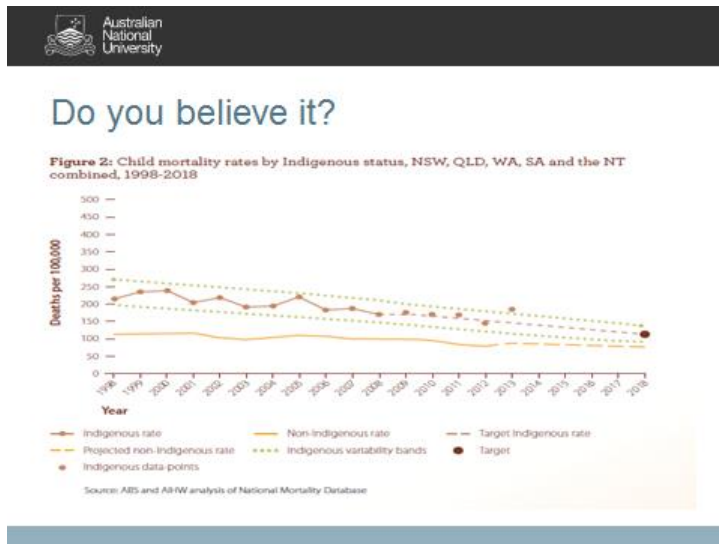
Questions to ask about the data

- Is this real?
  - Are the results statistically significant?
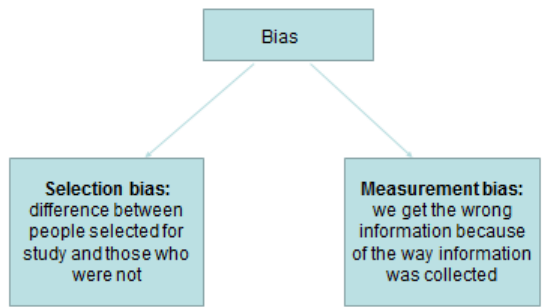 - Is there confounding?
  - Are the results biased?

What is bias?

- Systematic error.
- Happens when there's a difference between survey results and what's happening in the real population

What are the two major types of bias?

What biases do you think are occurring in these mortality figures?

Figure 2: Child mortality rates by Indigenous status, NSW, QLD, WA, SA and the NT combined, 1998-2018

Figure 2: Child mortality rates by Indigenous status, NSW, QLD, WA, SA and the NT combined, 1998-2018
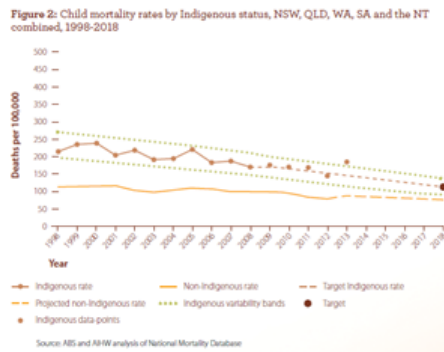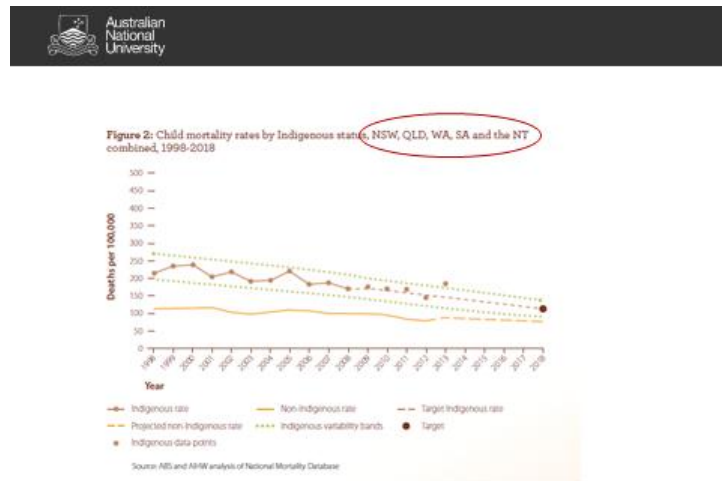
What kind of bias do you think this is?

- Is it selection or measurement bias?
  - Selection bias because ACT, VIC and TAS have been excluded i.e we have selected a non-representative group into our study
- Why are these States and Territory not included?
  - They have been excluded because of an error in measurement (i.e. error in Indigenous status being recorded)

Incomplete identification of Indigenous status

- Under-reporting of Indigenous status

- Four jurisdictions (QLD, WA, SA and NT) assessed as 'complete'

Why?

- Clients are not asked about their Indigenous status
- The standard question is asked inconsistently
- The answer is recorded inaccurately by the interviewer
- The data are not entered into databases accurately
- People don't identify

Case Study - Hepatitis A

Hepatitis A positive cases who identify as being Aboriginal and/or Torres Strait Islander (unpublished data, 2015).

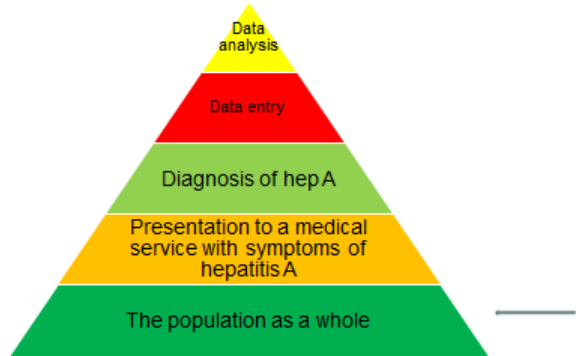| Aboriginal and/or Torres Strait Islander	INDIG STATUS						
	Aborigine	Torres St	Both Abor	Non-Indig	Not state	.	Total
No	0	0	0	1,492	0	0	1,492
Yes	435	122	35	0	0	0	592
.	0	0	0	0	4,664	1	4,665
Total	435	122	35	1,492	4,664	1	6,749

Case Study - Hepatitis A

Hepatitis A positive cases who identify as being Aboriginal and/or Torres Strait Islander (unpublished data, 2015).

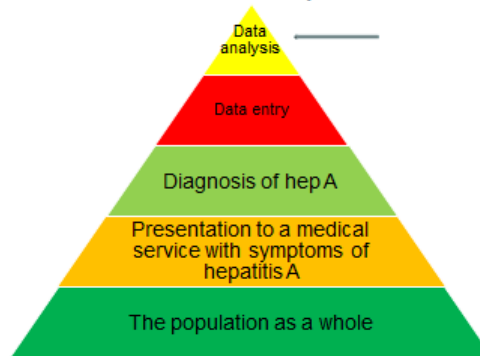| Aboriginal and/or Torres Strait Islander	Aborigine	Torres St	Both Abor	Non-Indig	Not state	.	Total
No	0	0	0	1,492	0	0	1,492
Yes	435	122	35	0	0	0	592
.	0	0	0	0	4,664	1	4,665
Total	435	122	35	1,492	4,664	1	6,749

Steps where identification process falters

Steps where identification process falters

What type of bias do you think is happening in the Hep A study?

How do you ask the question?

Example of FluMum cohort study workbook/questionnaire for participants who are asked if they identify as being Aboriginal and/or Torres Strait Islander.

		No	AB	TSI	B^{oth}	Dcl
18.01	Are you of Aboriginal or Torres Strait Islander origin? (At SIMum)	No	AB	TSI	Both	Dcl
18.02	Is your baby of Aboriginal or Torres Strait Islander origin? (At SIBaby)	No	AB	TSI	Both	Dcl

Case Study ii- Influenza in pregnancy

FluMum study participants who identify as being Aboriginal and/or Torres Strait Islander (unpublished data)2012-2014.

Aboriginal and/or Torres Strait Islander	Freq.	Percent	Cum.
0	6,945	97.13	97.13
1	205	2.87	100.00
Total	7,150	100.00	

Case Study ii- Influenza in pregnancy

FluMum study participants who identify as being Aboriginal and/or Torres Strait Islander (unpublished data)2012-2014.

Aboriginal and/or Torres Strait Islander	Freq.	Percent	Cum.
0	6,945	97.13	97.13
1	205	2.87	100.00
Total	7,150	100.00	

Measurement bias

- Data collection
- Tool (questionnaire)
- Person recording or interviewing
- Data entry

Group exercise

- What are the implications of using results from this Hep A study?

- Split into group and discuss

Some implications of under-reporting?

- Limits ability to compare across states and services
- We don't know if the characteristics of the people not being captured as Aboriginal and/or Torres Strait Islander are different
- Difficult to measure the gap between Indigenous and non-Indigenous Australians
  - Can lead to an underestimation of the gap difference
- Limits policy makers in understanding what works to overcome indigenous disadvantage and improve health outcomes

Recap

- What have you learnt in today's lesson?
- What was the most important thing you have learnt?
- What was the least important thing you learnt?

Recap – what does this all mean?

- Understand where your data are coming from
  - Bias
  - Chance
  - confounding

Recap – what does this all mean?

- All datasets have their limitations
- Be aware of the limitations that may come with the data
- Report limitations when reporting your findings

Think about selection and measurement bias…

7.   Publication

Outbreak investigation report of Salmonella Typhimurium following consumption of Korean style sushi in Southside Brisbane, January 2015.

Authors

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Key words

Korean sushi, Kimbap, *Salmonella*, Typhimurium, Brisbane, laboratory confirmed

Abstract

On 15 January 2015 the Metro South Public Health Unit Brisbane, received notification

of multiple people presenting to health care facilities with gastrointestinal illness

symptoms. All patients experienced symptoms following consumption of Kimbap

(Korean sushi) purchased from multiple food outlets in Brisbane. Laboratory analyses

of faecal samples confirmed *Salmonella* Typhimurium as the organism with similar

MLVA patterns consistent for cases. Twenty-two cases were hospitalised including

seven children. Supply of the product ceased on Friday 16 January 2015 and there

were no further reported cases of illness. This short report describes the

epidemiological, laboratory and environmental health investigations from the

outbreak.

Background

Identification of an outbreak

On Thursday 15 January 2015 the Metro South Public Health Unit (MSPHU) in Brisbane received notification that five people had presented to one General Practitioner with gastrointestinal symptoms. A further four people with similar symptoms presented to a hospital emergency department in southern Brisbane. Verbal and written reports indicated all cases had experienced abdominal cramps, diarrhoea and vomiting following the consumption of Kimbap purchased from multiple food outlets in Brisbane. Faecal specimens were sent to the public health microbiology laboratory at Forensic and Scientific Services (QHFSS). *Salmonella* Typhimurium was confirmed and subsequently genotyped using Multiple Locus Variable-number tandem repeat Analysis (MLVA) demonstrating patterns were similar for all cases.

The purpose of the outbreak investigation was to determine the source of *Salmonella* Typhimurium infection and instigate control measures to prevent further illness from occurring in the community. A communication strategy was devised to deal with interest from the media and those concerned about the outbreak in the wider Brisbane community.

Methods

A case was defined as any person who consumed Kimbap from 13 to 16 January 2015 and subsequently developed diarrhoea and/or vomiting and/or stomach cramps within the incubation period for *Salmonella*. Cases were interviewed using Queensland Health 'Suspected' and 'Alleged' Foodborne illness outbreak hypothesis generating

questionnaires.[1] Three-day food histories were used in the hypothesis generating

interview process.

If *Salmonella* was cultured from faecal specimens they were serotyped. If subsequently

identified as Typhimurium, they were genotyped using the MLVA method.

The environmental health investigation included joint inspections by MSPHU and

Brisbane City Council to numerous retail food outlets known to sell Kimbap. An

inspection of the residential home of the Kimbap producer was conducted as it was

thought the product was being prepared in the dwelling. These inspections involved

food sampling and environmental swabbing of food preparation surfaces. All food

samples and environmental swabs obtained were sent to the laboratory for bacterial

analysis. A descriptive data analysis was conducted on the case series using Stata

version 12.1 (StataCorp, Texas, USA) and EpiInfo version 7.

Description of outbreak

There were 85 confirmed cases in this outbreak. Most cases (96%) were of Asian

ethnicity and 98% resided in Brisbane. Initially it was difficult to contact people for

further information due to severity of their illness and language difficulties. All had

consumed Kimbap between Jan 13 and Jan 16 January 2015 and developed

gastrointestinal symptoms with onset dates from 13 to 16 January 2015 (Figure 1). Five

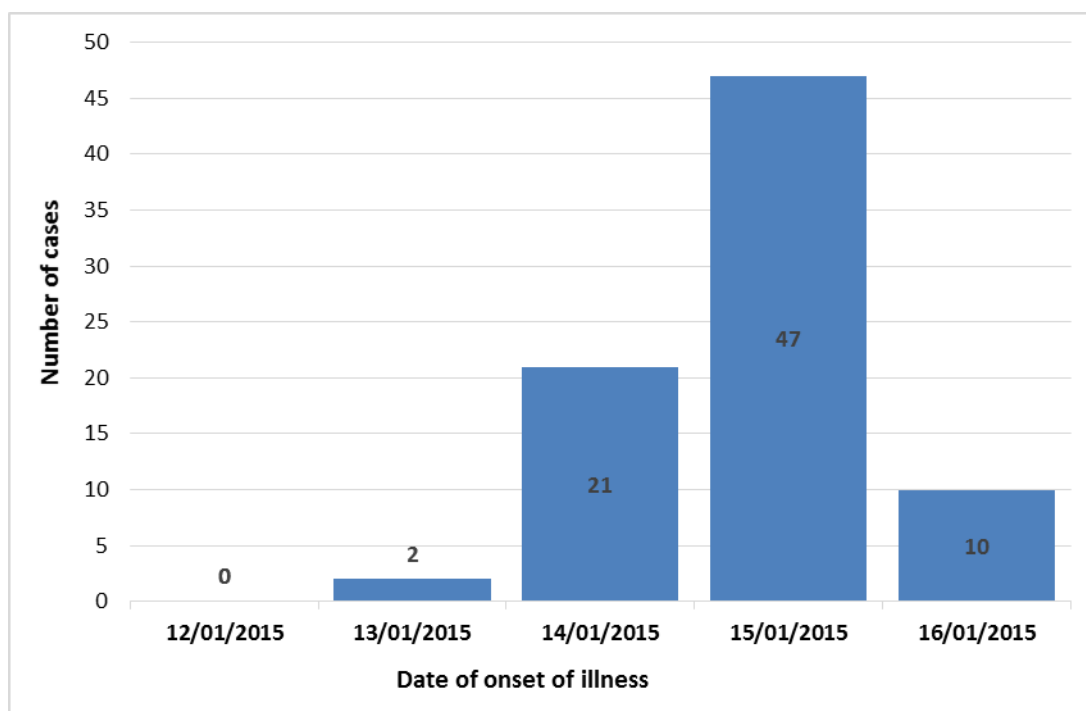cases are excluded from this figure due to missing data.

Figure 1: Confirmed cases of *Salmonella* Typhimurium by date of onset of illness, South Brisbane, January 2015.

The final median incubation period from consumption of the Kimbap to onset of illness was 15 hours (range 6 to 52 hours). Of the 85 confirmed cases, 44 provided faecal specimens that were positive for either *Salmonella* Typhimurium MLVA 03-12-11-12-524 or MLVA 03-13-11-12-524.

Of the 85 cases 60% were female and the median age was 31 years (range <1 – 66 years). Twenty-two were hospitalised including seven children. Symptoms reported by cases included; diarrhoea (100%), stomach cramps (91%), fever (86%), headache 74%) nausea (66%) and vomiting (54%). Three people reported bloody diarrhoea.

Kimbap was known to be purchased from 22 Korean food retailers throughout Brisbane in January 2015. Cooked rice and sesame oil was contained in all pre-

packaged sushi. Other fillings in Kimbap reported by cases were eggs (69%), tuna (65%) a variety of mixed vegetables (63%), ham (52%) and seafood extender (10%).

Laboratory and environmental investigations

Leftover food samples of Kimbap collected from one retail food outlet were positive for *Salmonella* Typhimurium MLVA 03-12-11-12-524. Pre-prepared Kimbap was not found at the owner/operator's residential premises during this inspection however commercial quantities of food items were obtained that would normally be used to prepare Kimbap.

Results from the environmental health inspections led to a range of outcomes including; suspension and surrendering of food licences, identification of poor food hygiene practices and identification of premises with no food licences.

The owner/operator was unable to be located therefore MSPHU was unable to obtain any further information to instigate traceback of food suppliers.

Discussion

Kimbap was sold pre-made, pre-packaged and contained multiple high-risk food items known to potentially cause Salmonellosis.[2] Each Kimbap roll contained multiple ingredients [3] and since the producer was never able to be investigated it was not possible to determine the primary source of the contaminated food. Cross contamination during the preparation process was also a possibility.

Conducting interviews for cases in this outbreak proved challenging due to severity of

illness and communication difficulties. Interpreters were not used during the interview

process therefore it is possible some misinterpretation could have occurred during the

completion of questionnaires. Nevertheless, recall error for cases was unlikely due to

the severity of symptoms experienced, consumption of food from pre-packaged and

clearly labelled containers, and the minimal time frame between onset and notification

of illness to being interviewed by public health staff. Media coverage[4] may have

prompted more people experiencing gastroenteritis symptoms to seek medical

attention, potentially identifying more cases.

This outbreak occurred at a time of increased background incidence of Salmonella: the

Queensland OzFoodNet Enteric Disease Surveillance Report for 24 January 2015

indicates that notifications were 2.2 times higher than the preceding 5 year mean for

this time period; 55% of cases serotyped as Salmonella Typhimurium and seven

outbreaks of Salmonella Typhimurium infection requiring investigation had been

recorded in South East Queensland from mid-December 2014[5].

Public Health Implications

This outbreak affected over 100 members of a Brisbane Asian community. The degree

of illness experienced by cases was severe with multiple hospitalisations including

seven children. These factors precipitated wide spread media interest in the outbreak.

Final numbers of affected individuals from this outbreak are unknown as some cases

refused an interview and/or specimen collection.

Efforts to control this outbreak were successful. Evidence indicated the aetiological

agent responsible for illness was *Salmonella* Typhimurium. The likely vehicle of

transmission of infection was Kimbap, distributed by one producer to multiple food

retail outlets in Brisbane. Supply of product ceased on Friday 16 January, 2015 and no

further reported cases of illness ensued.

Acknowledgements

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   2015